The New England
Journal of Medicine

Copyright, 1952, by the Massachusetts Medical Society

Volume 246 MARCH 13, 1952 Number 11

CARCINOMA OF THE RIGHT COLON*

BENTLEY P. COLCOCK, M.D.†

BOSTON

THIS study is based on 242 patients who were operated on between 1930 and 1950 for carcinoma of the right colon. This group includes patients with carcinoma of the cecum, the ascending colon and the hepatic flexure. Judging from a previous study[1] of 1457 patients with cancer of the large bowel and rectum, this group represents approximately 12.76 per cent of all patients with cancer of the colon and rectum. Carcinomas at any point in the ascending colon, including the hepatic flexure, may properly be grouped with carcinomas of the cecum, as all these lesions tend to metastasize to lymph nodes along the ileocolic artery, and a wide resection of the right colon and terminal ileum is indicated for any malignant lesion in this segment of the large bowel.

SEX AND AGE

Rankin and Graham[2] have stated that carcinoma of the colon usually occurs in the male in a ratio of approximately 2 to 1. Very little sex difference was found in this group of patients with carcinoma of the right colon; 125 occurred in males and 117 in females. The patients ranged in age from 27 to 91 years. Eleven patients, or 4.6 per cent, were under forty years of age; 32, or 13.2 per cent, were over seventy years of age (Table 1). That these patients over seventy years of age withstand operative removal of their lesions remarkably well is shown by the fact that in the 24 (75 per cent of this group over seventy) who had resection of their malignant lesions only 1 postoperative death occurred, and no deaths occurred in the group of 19 who were operated on after 1940.

TABLE 1. *Ages of Patients with Carcinoma of the Right Colon.*

No. of Patients	Age	Percentage
	yr.	
11	27–40	4.6
199	40–70	82.2
32	70+	13.2

SYMPTOMATOLOGY

An accurate record of the onset of symptoms was available in 169 cases. Pain was the most common symptom and occurred in 94, or 55.6 per cent (Table 2). The pain may be localized to the right lower quadrant or may take the form of a generalized discomfort referred to the right side of the abdomen. In the beginning it is frequently intermittent in character. It was significant that in 53 patients, or 31.4 per cent, pain was the only symptom present at the time the diagnosis was made.

TABLE 2. *Symptomatology of Carcinoma of the Right Colon.*

Symptoms	No. of Patients	Percentage
Pain	94	55.6
Change in bowel habit	62	36.7
Loss of weight and anemia	56	33.1

In spite of the fact that carcinoma of the right colon is frequently a large ulcerating type of growth with less tendency to encircle the lumen and produce constriction than carcinoma of the left colon, a change in bowel habit was the second most common symptom and occurred in 62 patients, or 36.7 per cent. In 52 patients the change in bowel habit took the form of increasing constipation, and in 27 it developed to the point of producing the signs and symptoms of intestinal obstruction, such as pain, distention, nausea and vomiting. In 10 patients diarrhea was the initial symptom. Loss of weight and anemia were the next most common symptoms and occurred in 56 patients, or 33.1 per cent. The fact that in 19 patients or 11.2 per cent of the entire group of 169, loss of weight and anemia were the only symptoms present emphasizes again that an asymptomatic carcinoma of the right colon should always be ruled out in any patient who has an unexplained anemia. Gross blood was present in the stool in only 18 patients (10.6

*Read by title at a meeting of the New England Surgical Society, York Harbor, Maine, September 21, 1951.

This study was supported in part by a grant for statistical study from the American Cancer Society (Massachusetts Division), Incorporated.

†Surgeon, Lahey Clinic, New England Deaconess and New England Baptist hospitals.

per cent), and a palpable mass was found in only 10 patients (5.9 per cent).

Unfortunately, there was little evidence from this study that appreciable progress is being made in the early diagnosis of carcinoma of the right colon. Although the average duration of symptoms decreased from twelve months for those patients operated on between 1930 and 1940 to 7.8 months for those operated on between 1940 and 1950, the higher average in the first group is probably accounted for by a few patients who had unusually long periods of symptoms before the diagnosis was established. Of the patients operated on in the first decade, 61.2 per cent had symptoms for three months or less, whereas only 39.1 per cent of those patients operated on between 1940 and 1950 had symptoms for three months or less. Moreover, 30.3 per cent of those operated on between 1930 and 1940 showed local fixation of the growth at the time of operation, whereas this finding had increased to 40.7 per cent for those patients operated on between 1940 and 1950.

As has been pointed out by Estes,[3] Pfeiffer[4] and others, it seems that more significance must be attached to the single symptom of persistent abdominal pain or discomfort. More patients with abdominal pain or distress must be submitted to a barium-enema examination without waiting for a change in bowel habits, the presence of blood in the stools or the development of a mass in the right side if the number of patients is to be increased in whom an early diagnosis of carcinoma of the right colon can be made. An irregular filling defect in the cecum or ascending colon on barium-enema examination confirms the diagnosis. If the barium-enema examination is reported as negative and the symptoms of right-sided pain, change in bowel habits or unexplained anemia persist, it should be repeated in six to eight weeks. Tuberculosis of the ileocecal region is the chief nonmalignant lesion likely to be confused with carcinoma of the cecum. The hyperplastic type may present an identical picture on barium-enema examination. The ulcerative type usually exhibits more irregularity of the filling defect, and foreshortening of the cecum is a significant finding in tuberculosis of this type. A retrocecal appendix that has been the site of previous inflammation may produce a persisting filling defect in the cecal outline on barium-enema examination. Exploratory laparotomy should be seriously considered in any patient over the age of forty who presents a persistent filling defect of the cecum with unexplained abdominal symptoms.

Preoperative Preparation

On admission to the hospital these patients are carefully examined for the presence or absence of obstruction. Although obstruction secondary to carcinoma of the right colon occurs less frequently than with malignant disease of the left colon, dilatation of the cecum and small bowel may occur secondary to constrictive lesions of the ascending colon and hepatic flexure. At times carcinoma of the cecum may produce obstruction of the small bowel as a result of occlusion of the ileocecal valve.

If obstruction is not present these patients are given 1½ ounces of magnesium sulfate on admission. Colonic irrigations are given twice a day to empty the colon from below. The patients are given 2 gm. of sulfathalidine four times a day, and beginning forty-eight hours before the operative procedure they also receive 1 gm. of streptomycin daily. Certainly, the use of sulfathalidine and sulfasuxidine, along with penicillin, streptomycin, aureomycin and the other antibiotics, has contributed greatly toward lowering the mortality in colon resections and also has permitted the increasing use of the one-stage operative procedure. It should be emphasized, however, that sulfone derivatives and the antibiotics do not take the place of careful mechanical cleansing of the colon during this preoperative period. If there are signs of obstruction a Miller–Abbott tube is immediately passed to decompress the small bowel. If marked dilatation of the cecum and ascending colon is present, the Miller–Abbott tube must not be relied on for decompression. If the ileocecal valve remains closed in these patients, perforation of the cecum may occur in spite of adequate decompression of the small bowel. Cecostomy should always be seriously considered in any patient with a marked dilatation of the cecum and proximal colon. The day before the scheduled operation we routinely insert a Miller–Abbott tube in all patients with carcinoma of the right colon whether or not an obstruction is present. All these patients have an anastomosis between the small bowel and colon after the resection of their growth, and with the tube well down in the small bowel the area of anastomosis can be kept decompressed until the passage of flatus by rectum and the absence of distention indicate that the anastomosis is functioning normally.

In addition to preparation of the colon, the general condition of the patient should be carefully checked before operation is performed. Many of these patients have a marked anemia on admission and require several transfusions before their erythrocyte count and hemoglobin are brought to satisfactory levels for operation. The hemoglobin should be at least 70 per cent and the white cells should number over 3,500,000 before operation is performed. Transfusions of whole blood constitute the most satisfactory means of restoring the low serum-protein levels so frequently found in patients with cancer of the colon. Restoration of serum proteins to normal or near normal is important in the prevention of edema at the site of anastomosis. Since many of these patients are sixty years of age and over, it is important to check

their kidney function; if there is any question of cardiac impairment, a careful evaluation should be made during the preoperative period.

Operative Procedure

Laparotomy only was carried out in 14 patients, 26 patients had a palliative ileotransverse colostomy and 202 patients were submitted to resection (Table 3). Of these 202 patients a modified Mikulicz type of procedure was carried out in 142, or 70.3 per cent. Fifty-four patients, or 26.7 per cent, had a one-stage resection with primary anastomosis, and 6 patients, or 2.9 per cent, had a two-stage procedure consisting of an ileotransverse colostomy followed by subsequent resection of the right colon and terminal ileum. The over-all operability rate was 83.5 per cent. The use of antibiotics, the more extensive use of blood replacement and, particularly, the increased emphasis placed on careful preoperative preparation of the colon have permitted a steadily increasing use of a one-stage procedure for resection of the right colon. This is evidenced by the fact that of the last 50 patients in this series resection was carried out in 44 patients (operability rate, 88 per cent); all 44 patients had a one-stage resection with primary anastomosis Table 4). The fact that the operability rate was as high as it was (78.4 per cent) for the period between 1930 and 1940 before sulfanilamide and the antibiotics were available and when the replacement of blood and the preoperative preparation of the colon were less adequate than indicated today was due in large part to the use of the modified Mikulicz procedure. Many extensive growths were resected by this type of operative procedure that would have been considered too hazardous for a one-stage resection at that time.

Table 3. *Operative Procedures for Carcinoma of the Right Colon.*

Procedure	No. of Patients
Laparotomy only	14
Ileotransverse colostomy	26
Resection	202 (83.5%)

Table 4. *Type of Resection Used in 202 Cases of Carcinoma of the Right Colon.*

Type of Resection	No. of Patients	Percentage
Modified Mikulicz resection	142	70.3
One-stage resection, primary anastomosis	54	26.7
Two-stage resection with anastomosis	6	2.9

Technic of One-Stage Right Colectomy

Spinal anesthesia is used routinely at the clinic for all patients with carcinoma of the colon. Intravenous infusions are started at the ankle before the operative procedure is begun, and at least 500 cc. of blood is given during the operation. Either a mid-right-rectus or right-paramedian incision is used. The abdomen is carefully explored for evidence of metastases and the colon itself is palpated carefully to rule out the presence of a second primary lesion in the left colon or sigmoidal area. In our experience two primary lesions are found in 4 per cent of patients with carcinoma of the colon. Mobilization of the cecum and ascending colon is then started by incising the line of fusion between the parietal and visceral peritoneum. If the lesion is fixed to the lateral abdominal wall, that portion of the parietal peritoneum and underlying musculature is removed along with the lesion. The bowel with its mesentery is mobilized medialward, the right ureter and the retroperitoneal portion of the duodenum being carefully reflected (Fig. 1). Occasionally it may be necessary to resect a portion of the anterior wall of the duodenum when it is invaded by a lesion of the hepatic flexure. The right ureter is easily identified by its course parallel and just medial to the right spermatic or ovarian vessels. The ileocolic, the right colic and the right branch of the middle-colic arteries are divided close to their origin, as large and deep a segment of the mesentery of the right colon and ileum as possible being removed (Fig. 2). The right half of the omentum is removed with the right half of the transverse colon. After removal of the growth with its mesentery, the ileum is anastomosed to the distal transverse colon by side-to-side, end-to-side or end-to-end sutures (Fig. 3 and 4). I prefer

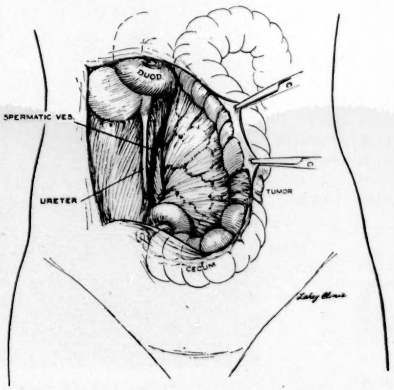

Figure 1. *One-Stage Right Colectomy: Mobilization of the Colon. (Reproduced from Colcock,[6] by Permission of the Publishers.)*

an end-to-end anastomosis between the terminal ileum and transverse colon, using two rows of interrupted silk sutures.[5] If the colon has been adequately decompressed and the ileum divided obliquely, any remaining disparity in the size of the lumens of the large and small bowel can be corrected as the anastomosis progresses. After completion of the anastomosis the mesentery is carefully approximated on each side and the right lumbar gutter is completely reperitonealized. We believe that reperitonealization of all raw surfaces whenever possible is an important factor in the prevention of postoperative complications.

One hundred thousand units of penicillin is placed in the peritoneal cavity and the wound is closed in layers or by far-and-near wire sutures inserted through the fascia, muscle and peritoneum as described by Jones and his associates.[6] The Miller–Abbott tube is placed on suction for forty-eight hours and removed when the presence of peristalsis and the passage of gas by rectum indicate that it is no longer necessary. Patients are allowed

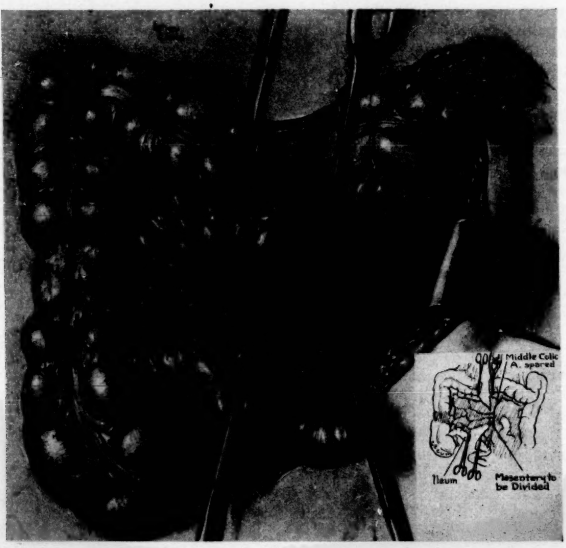

FIGURE 2. *The Extent of Resection in One-Stage Colectomy.*

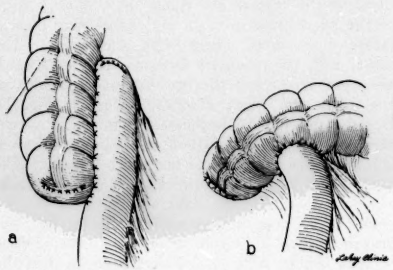

FIGURE 3. *Restoration of Intestinal Continuity. (Reproduced from Colcock,[6] by Permission of the Publishers.)*

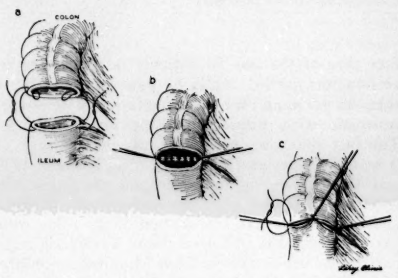

FIGURE 4. *Technic of Anastomosis. (Reproduced from Colcock,[6] by Permission of the Publishers.)*

out of bed at any time after the first forty-eight hours, and their average stay in the hospital is currently about ten days.

Operative Findings

Twenty-five patients (10.3 per cent) already had liver metastases at the time of operation. A palliative resection was carried out in a few of these patients, but usually a side-to-side ileotransverse colostomy was performed to prevent the development of intestinal obstruction. At the present time a palliative resection is carried out in all cases except those with the most extensive growths. Palliative resection of the primary tumor, especially of the massive ulcerating type so frequently seen in the cecum and ascending colon, is often well worth while even in the presence of early liver metastasis. Resection will frequently give these patients a considerable period of relief from the pain and abdominal discomfort associated with this infiltrating, adherent malignant growth.

Local fixation of the growth is a common finding in patients with carcinoma of the right colon. In 90 patients (37.2 per cent) the malignant tumor was fixed to the posterior or lateral abdominal wall. Although local fixation of any malignant growth usually indicates a far advanced growth and 15 (16.7 per cent) of these 90 patients also had metastases in the liver, the presence of local fixation should not be considered a contraindication to resection in patients with carcinoma of the right colon. Omitting those patients who already had gross metastases to their liver, 58.7 per cent of the patients with local fixation of their malignant growth were found on subsequent pathological examination of the resected specimen to show no evidence of metastases to the mesenteric lymph nodes or evidence of blood-vessel invasion.

The presence of palpable lymph nodes in the mesentery does not necessarily indicate a poor prognosis in patients with carcinoma of the right colon. In 81 patients (33.4 per cent) the mesenteric lymph nodes were noted as being enlarged and palpable. Eliminating 10 patients who already had metastases to the liver, only 28.1 per cent of the remaining 71 patients with palpable nodes proved on pathological examination to show actual metastases to the lymph nodes of the resected specimen. The difficulty of attaching any significance to palpably enlarged mesenteric nodes without microscopical examination is also shown by the fact that of the 79 patients who were actually later found to show metastases to the adjacent mesenteric lymph nodes, 54, or 68.3 per cent, were not recorded as having palpable nodes at the time of operation.

Pathology

On examination of the 202 resected specimens, 153, or 75.7 per cent, were adenocarcinoma, 29, or 14.4 per cent, were carcinoma simplex and 10 were mucinous carcinoma; 10 were classified as malignant adenoma (Table 5). Seventy-nine specimens, or 39.1 per cent, showed metastases to the mesenteric lymph nodes; 42 specimens, or 20.8 per cent, showed blood-vessel invasion on microscopical examination; 18 or 42.8 per cent of the 42 patients showing blood-vessel invasion did not have involvement of the mesenteric lymph nodes. It is of interest that 17 specimens (from 8.4 per cent of all patients who were submitted to resection) showed associated mucosal polyps (Table 6). It is now generally accepted that these mucosal polyps definitely are potentially malignant lesions and that most carcinomas of the colon and rectum probably arise in pre-existing mucosal polyps.

Table 5. *Pathological Findings in Cases of Carcinoma of the Right Colon.*

Finding	No. of Patients	Percentage
Adenocarcinoma	153	75.7
Carcinoma simplex	29	14.4
Mucinous carcinoma	10	4.9
Malignant adenoma	10	4.9

Table 6. *Pathological Findings.*

Findings	No. of Patients	Percentage
Metastases to mesenteric lymph nodes	79	39.1
Blood-vessel invasion	42	20.8
Associated mucosal polyps	17	8.4

Since in our experience mucosal polyps are multiple in 42 per cent of the patients in whom they are found, any patient who has a polyp or an actual cancer should have careful examinations of the remaining large bowel and rectum at regular intervals to determine whether other premalignant lesions are present. It should be remembered that only one third of the patients who have benign polyps in their colons or rectums will have bleeding or any other symptoms referable to the tumor.[7, 8]

Mortality

Twenty-one of 202 patients who had resection of their malignant tumors died in the hospital after operation. This is an operative mortality of 10.4 per cent. In the last 100 resected cases, which represent approximately one half of the entire group, there were 3 deaths, or an operative mortality of 3 per cent (Table 7). One death was due to uremia, 1 to coronary occlusion and 1 to peritonitis.

Table 7. *Mortality.*

	No. of Patients	Percentage
Total number of resections (202)	22	10.4
Last 100 cases	3	3.0

None of the 3 deaths followed a one-stage resection with primary anastomosis. Although these 3 deaths occurred in the period before the antibiotics were available, in only 1 patient could they possibly have prevented death.

Follow-up

Out of this group of 202 patients who had resections of their malignant tumors, 120 patients survived their operation and had their resection over five years ago (before 1946). Fifty-two of the 120 patients are alive and well without evidence of recurrence five to ten years after the operative procedure. Fifty-one patients died of recurrence of carcinoma. Nine patients died from other causes and at the time of their deaths did not have recurrence of carcinoma, so far as could be determined. Since 13 per cent were over seventy years of age, an appreciable number could be expected to die from other causes. Whether or not they were cured of their malignant disease cannot be determined. Eight patients were lost to follow-up. If the patients who were lost to follow-up and the patients who died from other causes were considered to have recurrence of carcinoma, the five-year survival rate is 43.3 per cent. If the patients lost to follow-up and dying from other causes are eliminated as unknown factors the survival rate in the remaining 103 patients was 50.5 per cent (Table 8). Our previous impression concerning the seriousness of blood-vessel invasion found in the microscopical examination of the resected specimen was not supported by the small number of patients showing this finding in this series. Of the 12 patients with blood-vessel invasion who were followed five years or more, 6 were alive and well. This is a survival rate of 50 per cent, which is comparable to the overall survival rate for the entire group. Of the 41 patients who showed metastases to the mesenteric lymph nodes in the resected specimen, survived their operations and were not lost to follow-up, 11 were alive and well five or more years after operation. This is a five-year survival rate of 26.8 per cent, which is in line with our previous finding that metastatic involvement of the mesenteric lymph nodes in the resected specimen cuts the survival rate almost in half in patients with carcinoma of the colon and rectum. It was of interest that of the 52 patients who survived five years or more after their operative procedure 25 per cent had local fixation of the growth at the time of operation.

Table 8. *Follow-Up Findings in Patients Followed Five to Ten Years and Either Living without Recurrence or Dead of Recurrent Carcinoma.*

	No. of Patients	Surviving 5 to 10 Years	
		no.	%
Total number of patients	103	52	50.5
With blood-vessel invasion	12	6	50.0
With metastases to mesenteric lymph nodes	41	11	26.8

Conclusions

Elderly patients withstand resection of the right colon for malignant disease reasonably well.

Carcinoma of the right colon should be suspected in any middle-aged person who has persistent right-sided abdominal distress or pain, even though there are no associated gastrointestinal symptoms. It should always be suspected in any patient who has an unexplained anemia.

Local fixation of the growth at the time of operation does not necessarily mean a poor prognosis.

A one-stage operative procedure can be carried out in cases of carcinoma of the right colon with a reasonably low mortality rate. Patients who have had a resection for carcinoma of the right colon should have careful follow-up proctoscopic and barium-enema examinations to rule out the presence of other mucosal polyps that might result in the development of a second malignant tumor. The five-year survival rate of patients with carcinoma of the right colon is approximately 50 per cent; it is cut almost in half when there is microscopical evidence of spread of the cancer to the mesenteric lymph nodes.

605 Commonwealth Avenue

References

1. Boehme, E. J., and Hanson, P. J. Carcinoma of colon and rectum: site of growth of 1,457 lesions. *S. Clin. North America* **26**:551, 1946.
2. Rankin, F. W., and Graham, A. S. *Cancer of Colon and Rectum: Its diagnosis and treatment.* 358 pp. Springfield, Illinois: Charles C Thomas, 1939.
3. Estes, W. L., Jr. Early diagnosis of cancer of colon. *Pennsylvania M. J.* **46**:1139-1142, 1943.
4. Pfeiffer, D. B. Discussion. *Pennsylvania M. J.* **46**:1142, 1943.
5. Colcock, B. P. Primary resection of colon. *S. Clin. North America* **29**:829-841, 1949.
6. Jones, T. E., Newell, E. T., Jr., and Brubaker, R. E. Use of alloy steel wire in closure of abdominal wounds. *Surg., Gynec. & Obst.* **72**:1056-1059, 1941.
7. Cattell, R. B. Surgical treatment of polyps of large intestine. *Am. J. Surg.* **76**:733-742, 1948.
8. Swinton, N. W., and Holt, J. H. Polyps of colon and rectum. *Surg. Prac., Lahey Clin.* Philadelphia: W. B Saunders Company, 1951. Pp. 391-405.

ACUTE EFFECTS OF INTRAVENOUS ADMINISTRATION OF A PREPARATION OF *VERATRUM VIRIDE* IN PATIENTS WITH SEVERE FORMS OF HYPERTENSIVE DISEASE*

NORMAN S. STEARNS, M.D.,† AND LAURENCE B. ELLIS, M.D.‡

BOSTON

THE pharmacology of Veratrum alkaloids has been reviewed recently[1] and several reports dealing with their clinical use have also appeared in the literature.[2-9] The purpose of the present investigation was to determine the relative safety of the intravenous administration of *Veratrum viride* to lower acutely the blood pressure in patients with severe hypertension associated with cerebral, cardiac and renal impairment. For this purpose a biologically standardized[10] reproducible mixture[10, 11] of alkaloidal substances from *V. viride*§ was administered intravenously 36 times to 25 patients.

SELECTION OF PATIENTS

The patients included in this study were classified in two groups: those with a malignant form of hypertensive disease (Patients 1-16; Table 1); and those with a severe form of hypertensive disease but less fulminating than that of Group 1 (Patients 17–25). Hypertensive neuroretinopathy characterized by papilledema, hemorrhages and exudates was considered requisite to the diagnosis of malignant hypertensive disease. Hypertensive encephalopathy (crisis) was present at the time of the initial infusion in Patients 1–12. Cerebral hypertensive arteriosclerotic disease as evidenced by residua of recent or old cerebrovascular accidents was present in 7 patients (1, 5, 12, 15–18). Laboratory evidence of impaired renal function, noted in 23 patients, was pronounced in 13 (Patients 1, 2, 4–8, 10–13, 16, 17). Renal disease was considered primary in 8 patients. Ten patients (3, 5, 10, 11, 16–19, 21, 22) with known recent or past congestive heart failure were on digitalis therapy at the time of the Veratrum infusion.

METHOD

A small syringe (1 or 2 cc.) was used to measure accurately 1.3 to 3.0 cc. of a stock Veriloid solution containing 0.4 mg. per cc. The drug was then diluted in a larger syringe with 10 to 20 cc. of 5 per cent dextrose in distilled water so that the predetermined dose per minute of Veriloid was contained in each 0.5 or 1.0 cc. of the infusion that was administered into the patient's antecubital vein. The rate of infusion was regulated manually. In actual practice the dose of Veriloid in microgm. per kg. per minute was administered over a thirty-second interval, and the blood pressure corresponding to that dose was determined thirty seconds later. Two persons were present during all infusions, one to inject the drug and the other to record the blood pressure and heart-rate changes.

Veratrum infusions were initiated at 2 different rates: a relatively rapid rate of from 0.88 to 1.1 microgm. of Veriloid per kg. per minute (employed in 16 trials) and a slow rate ranging from 0.6 to 0.68 microgm. per kg. per minute (employed in 20 trials). In the trials of the rapid rate, infusions were usually interrupted for one to three minutes when the blood pressure decreased more than 30 systolic or 20 diastolic during any two- to three-minute period. In trials of the slow infusion rate, all infusions were interrupted deliberately for two minutes after each seven-to-nine-minute period of drug administration and at any time that a blood-pressure fall greater than 30 systolic or 20 diastolic occurred. All infusions were interrupted or stopped whenever nausea or emesis occurred. In 8 of the trials (2b; 7e; 8c, d, e; 14b; 18; 23) the infusion followed within three to seven hours of previous oral administration of the same preparation.

Blood pressures were taken by the conventional cuff method at one- to three- minute intervals for several minutes of a control period, throughout all infusions at one-minute intervals and for varying periods at less frequent intervals after infusion. Control levels reported in Table 1 represent the lowest of the preinfusion determinations. With rare exceptions, the diastolic blood pressure was considered to be the level at which sounds completely disappeared. Pulse rates were determined at one- to three-minute intervals during all infusions. Electrocardiograms were taken periodically during 18 trials. In most patients the volume of urine output was recorded for varying periods before and after the Veratrum infusions.

RESULTS

Pertinent data correlating the rate and amount of Veriloid infusion with vasodepressor and heart-slowing effects of the drug are summarized in Tables 1 and 2. The results in the 8 trials that had been preceded by oral Veriloid administration were similar to those in which oral therapy had not previously been used.

The onset of vasodepressor effect occurred after a period of infusion that averaged between eight and fourteen minutes. Total infusion time averaged

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

†Instructor in pharmacology, Boston University School of Medicine; research associate in medicine, Harvard Medical School; Postdoctorate Research Fellow of the National Institutes of Health at the Thorndike Memorial Laboratory.

‡Assistant clinical professor of medicine, Harvard Medical School; assistant visiting physician, Boston City Hospital; associate physician, Thorndike Memorial Laboratory.

§The preparation of *Veratrum viride* used in this study was "Veriloid," which was generously supplied by the Riker Laboratories.

26 ± 12 minutes. There was a blood-pressure "overshoot" (continued fall in blood pressure after infusion of the drug was stopped) in most patients.

No specific attempt was made to test for reproducibility of vasodepressor effects of Veriloid in individual patients. Four patients were treated

TABLE 1. *Intravenous Veriloid Administration: Results of 36 Trials in 25 Patients.**

PATIENT TRIAL	INITIAL INFUSION RATE	ARTERIAL BLOOD PRESSURE			AMOUNT INFUSED		PULSE RATE	
		CONTROL	AT END OF INFUSION	LOWEST LEVEL	TO FIRST BLOOD-PRESSURE FALL	TOTAL DOSE	CONTROL	MAXIMUM LOW
	microgm./kg./min.	*mm. Hg.*	*mm. Hg.*	*mm. Hg.*	*microgm./kg.*	*microgm./kg.*	*beats/min.*	*beats/min.*
1	0.92	200/130	180/120	80/60	11.0	11.9	—	—
2a	0.9	225/140	170/115	150/110	7.0	8.8	75	60
b	0.9	220/130	170/110	140/80	7.3	9.5	86	70
3	0.65	278/164	210/96	200/90	3.9	8.4	80	60
4	1.0	230/156	200/130	180/105	7.5	8.5	108	92
5	1.0	210/130	150/98	118/90	8.5	11.0	—	—
6	0.63	268/150	200/125	160/100	7.5	8.1	116	108
7a	0.96	280/160	242/114	220/110	6.7	19.2	100	90
b	0.96	252/130	190/100	180/86	10.6	12.0	92	76
c	0.96	270/150	228/120	160/90	11.5	19.2	92	84
d	0.96	250/140	228/116	150/80	11.5	15.4	84	76
e	0.96	282/144	272/134	160/80	10.6	10.6	84	80
8a	1.1	254/154	170/84	124/72	9.7	12.9	120	68
b	1.0	190/110	178/105	140/85	8.6	8.6	92	84
c	1.1	238/138	190/100	136/80	8.2	8.6	104	72
d	1.1	198/105	205/100	160/90	7.5	7.5	76	66
e	0.66	240/140	216/128	208/118	6.9	6.9	92	80
f	0.67	214/130	174/110	170/100	7.3	9.3	100	78
9	0.88	280/190	250/170	188/128	7.9	9.2	—	—
10	0.64	212/120	168/104	160/98	2.6	3.2	92	88
11	0.64	210/88	164/60	150/60	5.0	6.5	60	60
12	0.64	275/125	210/85	210/85	5.7	9.0	108	82
13	0.66	194/120	148/96	130/72	7.3	9.3	100	72
14a	0.64	230/110	150/88	130/78	3.7	6.7	92	64
b	0.64	200/100	170/80	128/74	5.7	5.7	64	46
15	0.64	240/114	198/100	148/88	3.8	5.1	72	64
16	0.64	246/122	200/104	174/94	5.7	9.0	100	80
17	0.65	210/118	170/82	146/80	3.9	7.0	72	52
18	0.66	236/140	176/105	157/80	4.0	7.3	120	120
19	0.6	230/130	180/100	160/88	3.6	7.9	92	64
20	0.64	280/140	236/116	162/92	5.2	9.1	76	60
21	0.64	260/140	175/100	125/85	5.1	9.6	94	70
22	0.64	240/130	200/100	192/100	2.6	11.5	96	80
23	0.66	200/100	162/80	138/70	5.3	5.3	58	48
24	0.65	210/116	170/86	160/80	7.2	12.5	82	68
25	1.0	260/160	200/130	160/110	5.0	9.0	130	75

*The time from infusion onset to infusion end was 26± 12 minutes. The time from infusion end to the appearance of the lowest blood-pressure level was 10 ± 9 minutes ("overshoot period").

†The first blood-pressure fall was considered to be the first drop in blood pressure amounting to more than 30 mm. Hg. systolic or 20 mm. Hg. diastolic.

Blood-pressure "overshoots" of relatively great magnitude occurred more frequently in the trials with rapid infusion rates. "Overshoot" values averaged 49 ± 29 systolic and 24 ± 17 diastolic for the rapid-infusion-rate trials as compared with 23 ± 20 systolic and 11 ± 8 diastolic for the slow-rate trials. These differences are significant. The duration of vasodepressor effect, judged by a fall greater than 50 systolic or 30 diastolic, ranged from three minutes to twelve hours and persisted from thirty to one hundred and twenty minutes after termination of infusion in 70 per cent of the trials. Veratrum-induced hypotension accompanied by signs and symptoms of collapse in one patient (Patient 1) was successfully counteracted by intravenous administration of neosynephrine.

The dose of Veriloid in microgm. per kg. that produced an initial drop (30 systolic or 20 diastolic) in blood pressure varied widely from patient to patient. Moreover, when the total hypotensive responses were correlated with their respective total doses of Veriloid, there was a wide scatter from patient to patient even though dosage was computed on the basis of body weight.

with more than one infusion at the same infusion rate; in 3 of these trials (2; 8a-d and 14) there was an increase in hypotensive response with increase in dose. In the fourth patient (Patient 7) the dose-response correlations were not consistent.

TABLE 2. *Vasodepressor Effects of an Intravenously Administered Preparation of* Veratrum Viride.

OBSERVATION	AVERAGES*
Control blood pressure	
Systolic	236±28.7 mm. Hg.
Diastolic	133±20.5 mm. Hg.
Maximum blood-pressure fall	
Systolic	79±27.6 mm. Hg.
Diastolic	44±17.0 mm. Hg.
Maximum blood-pressure fall (per cent of control)	
Systolic	33±10.4 %
Diastolic	32± 9.4 %
Blood-pressure "overshoot" (fall from level at infusion end to lowest level)	
Systolic	34±26.5 mm. Hg.
Diastolic	16±14.4 mm. Hg.
Dose that produced first blood-pressure fall greater than 30 mm. Hg. systolic or 20 mm. Hg. diastolic	6.7±2.5 microgm. kg.
Total dose	9.4±5.4 microgm. kg.
	588±183 microgm.

*Mean and standard deviation of 36 trials.

Vomiting occurred in 8 trials (1; 2a, b; 4; 6; 7e; 8d; 16) and nausea in 5 (5; 8a, 3; 17; 21). All but

3 of these patients were experiencing hypertensive encephalopathy and 9 had been suffering from nausea or vomiting within a matter of days prior to the administration of Veriloid. These symptoms were acute; they disappeared as the maximum effect of the drug passed off. In 5 patients there was a subsequent marked diminution or absence of gastrointestinal symptoms that had been present prior to the Veriloid therapy.

In 3 patients (8, 18, 23) vasodepression could not be accomplished with orally given Veriloid without attendant nausea and vomiting. In each of these patients a hypotensive effect unaccompanied by either nausea or emesis was obtained with the intravenous administration of the drug. In 2 of these patients the intravenous preparation was infused within six hours after the same preparation had been given orally. In the third patient (8) it was possible to demonstrate on several occasions the occurrence of nausea and emesis without vasodepression during oral administration of this Veratrum preparation and also the occurrence of a vasodepressor effect without nausea or emesis while it was being given intramuscularly. This patient was 1 of 2 in the series to whom the drug was given by this route for maintenance therapy; neither had any local reaction from the injections.

There was no clinical evidence of increased insufficiency of any of the vital organs during the hypotensive response. Myocardial insufficiency was not increased, there were no electrocardiographic signs of increasing myocardial damage and no coronary pain was induced. No patient showed any increase of cerebrovascular symptoms, and in no case was there a suppression of urinary output or an aggravation of nitrogen retention within twenty-four hours of the infusions.

Marked slowing of the heart rate was produced in relatively few patients; only 3 developed a bradycardia below 60 per minute. One patient developed transient auriculoventricular dissociation during infusion, with an auricular rate of 50 and a ventricular rate of 60 per minute.*

Symptomatic improvement accompanied or followed within two hours of the Veratrum infusion in 18 trials in 14 patients (1; 2a; 3; 6; 7c; 8a, b, c, d; 10; 12; 14a, b; 16–18; 20; 21). Patients with hypertensive encephalopathy showed the most favorable immediate responses, although these were not usually the most enduring. In 8 patients there was no improvement; in an additional 3, symptoms noted prior to infusion were so insignificant that it was impossible to judge an effect. The type of improvement is indicated in Table 3.

In most patients the symptomatic improvement outlasted initial vasodepressor responses by minutes to hours. In 9 patients it was possible to demonstrate relief of symptoms during infusion-induced vasodepression, a recurrence of symptoms with return of the pressure to control hypertensive levels and subsequent relief with vasodepression reinduced by supplemental intravenous or oral Veratrum administration. It is difficult to generalize about duration of effects induced by infusion alone, as Veriloid was administered orally to 13 patients within one to three hours after infusions and these patients had not yet shown a return to their control levels of hypertension in that interval.

TABLE 3. *Symptomatic Improvement Within Two Hours of Veratrum Infusion.*

SYMPTOMS OR SIGNS	NO. OF PATIENTS WITH SYMPTOMS	NO. OF PATIENTS IMPROVED
Headache or "fullness in head"	10	6
State of consciousness (lethargy to coma)	12	6
Visual disturbance (3 blurred, 2 "blind")	7(5+)	5
Restlessness	7	6
Muscle twitching	6	4
Acute epistaxis	1	1
Dyspnea (associated with congestive heart failure)	3	1
Development of sense of well-being	—	7

Five patients showed no evidence of clinical improvement immediately after infusions but subsequently did improve within twenty-four to forty-eight hours while on oral Veratrum therapy. In these patients, oral administration of Veriloid was started one to three hours after infusions of the drug. Doses of 1 mg. every three to six hours were effective in maintaining the lowered blood pressure that resulted from initial infusion therapy. Such results suggest that blood-pressure reduction may be achieved rapidly and maintained with relatively small oral doses of Veriloid in patients initially given the drug intravenously. In other patients it was necessary to raise the dose to 2 or 3 mg. every six hours within the first two days in order to achieve the desired effect.

It was difficult to evaluate the effect of this acute treatment on the duration of life, since the only feature of therapy common to the group was that the patients were treated intravenously with Veriloid at a time when most of them were critically ill. After infusions, therapy was varied but usually included salt restriction and oral Veratrum administration for periods of weeks to months. Ten patients, all with malignant forms of hypertensive disease, were considered to be in a terminal state at the time of initial drug infusion, and medical experience would have indicated that they might have lived but a matter of hours or days. Of these, 3 died within one week; 4 more died between the first and third weeks; and 2 died after one and five months. One is believed to be alive four months after infusion therapy. Of the 6 patients who had the malignant form of the disease but were not in such a terminal state, 1 survived one week, 1 two

*Since these results were compiled we have noted the occurrence of a nodal rhythm in an additional patient during intravenous Veriloid infusion. Two weeks later, while receiving intramuscular maintenance injections of Veriloid averaging 1 mg. every three hours, this patient developed Adams-Stokes attacks, with alternating cardiac asystole and ventricular fibrillation, and died. Both these patients were digitalized.

months and 1 four months. Three are alive and improved five to ten months after therapy. Of the severely hypertensive patients, 1 died after three weeks. Eight are alive after five months, and 5 of these are improved.

Discussion

The use of intravenously administered Veriloid, a standardized mixture of Veratrum alkaloids, was found helpful in the management of 25 patients with malignant and severe forms of hypertensive disease in whom excessively high blood-pressure levels warranted immediate vigorous treatment and also in patients who had previously failed to respond satisfactorily to oral Veratrum therapy. The drug infusion was effective in lowering the blood pressure in all patients and in relieving untoward symptoms in 8 of 12 patients with hypertensive encephalopathy (crisis). Unpleasant symptoms present in 11 additional patients without hypertensive encephalopathy were relieved in 6.

Veriloid can be given intravenously with relative safety to hypertensive patients even in the presence of severe renal, cardiac or cerebral functional impairment. The drug should be administered by infusion over a period of several minutes. An initial Veriloid infusion rate of from 0.6 to 0.68 microgm. per kg. per minute appears to be safe and effective. The blood-pressure changes should be followed carefully at one-minute intervals during infusion and at less frequent intervals for thirty minutes afterwards in order to encompass the entire "overshoot" period (time from end of infusion to maximum hypotensive response) for most patients. The effective total dose may vary from patient to patient, and in any single patient it should be computed on the basis of the vasodepressor response obtained during infusion of the drug. In general, the tendency toward a continued drop in blood pressure after infusion is stopped should be taken into account.

Slight to moderate heart-rate slowing, a desirable effect in some patients, was noted. True bradycardia attributable solely to intravenous Veriloid administration did not occur. In no case did heart-rate slowing necessitate terminating the infusion. A significant arrhythmia was noted in 1 of 36 trials.

Nausea or vomiting occurred in 10 patients, especially when the infusion rate was faster than that recommended, and in 7 patients with hypertensive encephalopathy. With the recommended method of administration, however, vomiting did not appear to be a sufficiently severe untoward side-effect to warrant limitation of the intravenous use of Veriloid. Vomiting occurred in 5 of the patients who appeared to benefit most from the Veriloid therapy.

In spite of encouraging symptomatic responses to Veriloid infusions, the survival data for the patients studied do not indicate that the course of hypertensive disease of this severe type was materially altered by the therapy except possibly in 3 patients.

Summary and Conclusions

Veriloid, a biologically standardized preparation of alkaloids from *Veratrum viride*, was administered intravenously 36 times to 25 patients with severe and malignant forms of hypertensive disease. The resulting pharmacologic and clinical effects are described and discussed. An apparently safe and effective method of infusing Veriloid for the induction of acute vasodepression is presented.

The intravenous administration of Veriloid seems to have a place in the treatment of the distressing symptoms of severe hypertensive disease, particularly the so-called hypertensive crisis or encephalopathy. If the drug is administered slowly, with a continuous checking of blood pressure, dangerous hypotensive collapse can be avoided. The dose must be regulated, however, on the basis of the patient's weight and his vasodepressor response during infusion of the drug.

References

1. Krayer, O., and Acheson, G. H. Pharmacology of veratrum alkaloids. *Physiol. Rev.* **26**:383-446, 1946.
2. Wilkins, R. W. Veratrum viride and essential hypertension. *New Eng. J. Med.* **242**:535-538, 1950.
3. Wilkins, R. W. Veratrum viride in hypertensive cardiovascular disease. *Mod. Concepts Cardiovasc. Dis.* **20**:89, 1951.
4. Freis, E. D., and Stanton, J. R. Clinical evaluation of veratrum viride in treatment of essential hypertension. *Am. Heart J.* **36**:723-738, 1948.
5. Freis, E. D., Stanton, J. R., and Moister, F. C. Assay in man of chemical fractions of veratrum viride, and identification of pure alkaloids germitrine and germidine as potent hypotensive principles derived from drug. *J. Pharmacol. & Exper. Therap.* **98**: 166-173, 1950.
6. Meilman, E., and Krayer, O. Clinical studies on veratrum alkaloids: action of protoveratrine and veratridine in hypertension. *Circulation* **1**:204-213, 1950.
7. Crumpton, C. E., et al. Hemodynamic actions of protoveratrine in essential hypertension. *J. Clin. Investigation* **30**:634, 1951.
8. Hoobler, S. W., Corley, R. W., and Kabza, T. G. Effects of protoveratrine on circulation in hypertension. *J. Clin. Investigation* **30**:651, 1951.
9. Meilman, E. Action of protoveratrine on renal function in hypertension. *J. Clin. Investigation* **30**:659, 1951.
10. Maison, G. L., and Stutzman, J. W. Bioassay for veratrum derivatives based on hypotension in dogs. *Arch. Int. Pharmacodyn.* **85**:357-368, 1951.
11. Stutzman, J. W., Maison, G. L., and Kusserow, G. W. Veriloid, new hypotensive extract of Veratrum viride. *Proc. Soc. Exper. Biol. & Med.* **71**:725-727, 1949.

STUDIES IN THE ARCTIC WITH THE FLICKER-FUSION NITROGLYCERIN TEST

A New Method of Evaluating Cardiovascular States

R. W. HOPKINS, M.D.*

LONGMEADOW, MASSACHUSETTS

STUDIES on the ability of the human being to distinguish a rapidly flickering light have been used in ophthalmologic research for well over a century.[1, 2] During the past ten years its use has extended beyond the laboratory of the ophthalmologist; it was recently proposed as a test for evaluating cardiovascular status in clinical patients.[3] This report is presented to call attention to its potentialities and to report a series of observations made in the Arctic.

The rapidity with which a nerve can respond to a rapid succession of stimuli has long been used as an index of its functional capacity. In the visual pathways of the central nervous system such a rapid succession of stimuli is provided by a rapidly flickering light. The ability to perceive a flicker appears to depend on the latent period of "on response" and the latent period of the "off response."[4] When the light source is rapidly interrupted, the light will appear constant or fused, as is the case with alternating current. As the rate is decreased the flicker becomes apparent. The point at which the flicker is barely perceptible is called the "critical frequency of flicker" or the "flicker-fusion threshold."[2]

This threshold may be ascertained in most persons with a remarkable degree of consistency. In nearly all cases tested we found a variation of less than 30 flashes per minute (f.p.m.) in threshold determinations after the subject had become familiar with the instrument. Somewhat similar results have been reported by other observers.[3, 5-7] The thresholds in this series ranged approximately from 2000 to 3000 f.p.m.

During recent years flicker-fusion thresholds have been studied in relation to various conditions other than optic states. Simonson and Enzer have found that the threshold tends to be lower with advancing years,[5] fatigue,[6] cardiac disease and hypertension.[7] They concluded that hypoxia of the central nervous system associated with these states was most likely responsible for the diminished flicker-fusion threshold. Krasno and Ivy substantiated this by testing subjects before and during periods in an altitude chamber. They found a marked decrease in threshold associated with hypoxia attendant on a simulated altitude of 18,000 feet.[8]

Measurement of flicker-fusion threshold has recently been facilitated by the development of a compact portable instrument in which the rate of the flicker is electronically controlled. This renders clinical testing practicable, whereas formerly it was feasible only in the laboratory. The flicker is produced by a cylinder rotating around a constant light source, with light projected on a screen 1.3 by 1.6 cm. In testing, the subject sits at a distance of 5 feet (1.6 m.), causing the image to fall only on the fovea centralis of the retina.

FLICKER-FUSION NITROGLYCERIN TEST

Recently Krasno and Ivy studied changes in flicker-fusion threshold after administration of nitroglycerin.[2] They postulated that with nitroglycerin normal subjects would develop passive congestion of retinal vessels, stasis of blood and a relative hypoxia. This would lead to a drop in the flicker-fusion threshold. In patients with a preexisting hypertonus of retinal vessels, relaxation following nitroglycerin administration would lead to a relative improvement in oxygenation and an increase in threshold. A rise following nitroglycerin would, therefore, be an "abnormal" response, whereas a fall would be considered "normal."

In testing, an initial flicker-fusion threshold was obtained in a subject at rest who had abstained from tobacco for six hours, and from whom alcohol and drugs had been withheld for twenty-four hours. After a two-minute rest 0.4 mg. of nitroglycerin was administered sublingually, and further readings were taken at two, four and six minutes. The maximum change in threshold noted during that time was used as the index of response to nitroglycerin.

In their series, all patients with hypertension or arteriosclerotic heart disease or both gave definite abnormal responses, with increase in threshold of 60 or more f.p.m. after nitroglycerin. In patients without evidence of cardiovascular disease a decrease in threshold was the rule, although there were several (approximately 13 per cent) who showed abnormal responses without other clinical evidence of an abnormal vascular system.

Our series comprised tests performed as described above in the Arctic over a period of several months. During that period the temperature ranged from a daily average of −15°F. in the spring to +45°F. in the summer. The subjects were living under camp conditions requiring them to be outdoors much of the time; in fact, the majority of them worked outdoors almost exclusively during the day. All persons examined had had thorough physical

*Field physician, Metcalf & Eddy and Alfred Hopkins & Associate (on leave of absence).

examinations and were apparently healthy and without clinical evidence of cardiovascular disease. Most were relatively young.

A total of 114 tests were performed on 81 subjects. Nine of these showed changes of less than 60 f.p.m., classified by Krasno and Ivy as showing "no change." If these 9 are eliminated, 65 of the remaining 105 (62 per cent) would be classified as normal responses, with a depression of the flicker-fusion threshold after nitroglycerin. Forty (38 per cent) would be considered abnormal. This is a much higher proportion of abnormal responses than that obtained by Krasno and Ivy. When temperature is taken into consideration, the reason for the difference seems apparent. When the average temperature during the day was 33° F. or above, only 7 abnormal tests were found in 39 subjects (18 per cent). This compares with the normals tested by Krasno and Ivy. Of those tested at 32°F. or below, however, 33 of 66 (50 per cent) showed an abnormal elevation of the flicker-fusion threshold (Table 1).

TABLE 1. *Results of 105 Flicker-Fusion Tests Made in the Arctic.*

TEMPERATURE °F.	PATIENTS SHOWING NORMAL RESPONSE	PATIENTS SHOWING ABNORMAL RESPONSE	TOTAL
−15 to +46 (total)	65 (62%)	40 (38%)	105
33 and above	32 (82%)	7 (18%)	39
32 and below	33 (50%)	33 (50%)	66
Subjects indoors 2 hours or more (32 and below)	27 (56%)	21 (44%)	48

Twenty-nine subjects were tested during the earlier colder period and again during the summer. Of these, the 13 who had previously shown normal responses remained normal. Of the 16 who had shown abnormal responses during the cold weather 13 became normal and only 3 remained abnormal. This tends to support our belief that the high proportion of abnormal responses is due to the cold environment. It is interesting that the abnormal results appeared almost as commonly in subjects who had been indoors for a period of two or more hours prior to the test as in those who were tested immediately after coming indoors. This would suggest that the hypertonus, which we believe is indicated by abnormal tests, is part of a general and prolonged reaction to the cold rather than an immediate and transient response to the given stimulus.

Absolute thresholds tended to be comparable to previously published figures, although there was a wide range of variation in each age group (Table 2).

Unfortunately, it was not possible to test subjects prior to their arrival in the Arctic for comparison of results in warm and cold climates.

DISCUSSION

Experience with the flicker photometer tends to corroborate the finding of Krasno and Ivy that a definite change of flicker-fusion threshold in response to nitroglycerin is the rule. We were not so fortunate as they, however, in that 9 of our 114 tests (8 per cent) showed changes, though seemingly definite, of less than 6 flashes per minute.

TABLE 2. *Flicker-Fusion Thresholds Observed in the Arctic.*

AGE yr.	NO. OF SUBJECTS	AVERAGE THRESHOLD f.p.m.	RANGE f.p.m.
20–30	55	2538	2040–3000
31–40	36	2485	2100–2850
41–50	18	2361	2070–2760
51–61	5	2292	1920–3030

These smaller variations were found with equal frequency in abnormal and normal responses.

In evaluating the principles underlying the test it seems logical to assume the following: When the ability to recognize flicker was improved after the administration of nitroglycerin (abnormal response), the initial function of the visual pathways was suboptimal or abnormal. Since the effect of nitroglycerin undoubtedly takes place through its relaxation of the arterial bed, the state of those vessels may be considered to have been at fault, or presumably they were in a state of hypertonus. Conversely, when the ability to recognize flicker is impaired by nitroglycerin, a previously normal vascular tree may be considered to have been rendered abnormal.

In the cases studied here the subjects showing abnormal responses, though clinically presenting no evidence of vascular impairment, presumably demonstrated a degree of subclinical hypertonus not readily observed by other means.

From these studies it might be further added that when the flicker-fusion nitroglycerin test is used in clinical evaluation, exposure of the patient to an abnormal environment must be considered when the results are interpreted. To eliminate similar possible variables in clinical testing we believe that basal testing performed in the morning, as are metabolic tests, might improve the reliability of the test.

It seems likely that the instrument may become valuable in evaluating and following various peripheral vascular diseases characterized by hypertonus of blood vessels such as Raynaud's disease, Buerger's disease and frostbite, as well as in hypertensive and cardiac patients. Further study with the flicker-fusion nitroglycerin test in these fields seems definitely indicated.

Summary

The flicker-fusion nitroglycerin test as proposed by Krasno and Ivy is described. In an abnormal response, found with vascular hypertonus, the flicker-fusion threshold is elevated after administration of nitroglycerin. In normal responses, — the type shown by most normal subjects, — the flicker-fusion threshold is depressed after nitroglycerin.

Subjects tested under cold-weather conditions showed a high percentage of abnormal responses, most pronounced when the environmental temperature was below freezing.

The flicker-fusion nitroglycerin test is of potential value in the study of various types of cardiac or vascular diseases in which hypertonus is an important factor. Further studies with this test are indicated.

1072 Longmeadow Street

References

1. Hecht, S. Nature of visual process. *Bull. New York Acad. Med.* **14**: 21-25, 1938.
2. Duke-Elder, W. S. *Textbook of Ophthalmology.* Vol. 1. St. Louis: C. V. Mosby Company, 1946. P. 948.
3. Krasno, L. R., and Ivy, A. C. Response of flicker fusion threshold to nitroglycerin and potential value in diagnosis, prognosis, and therapy of subclinical and clinical cardiovascular disease. *Circulation* **1**:1267-1276, 1950.
4. Bartly, S. H. *Vision: A study of its basis.* 350 pp. New York: D. Van Nostrand Company, 1941. Pp. 125 and 285.
5. Simonson, E., Enzer, N., and Blankstein, S. S. Influence of age on fusion frequency of flicker. *J. Exper. Psychol.* **29**:252-255, 1941.
6. Simonson, E., and Enzer, N. Measurement of fusion frequency of flicker as test for fatigue of central nervous system: observations on laboratory technicians and office workers. *J. Indust. Hyg. & Toxicol.* **23**:85-89, 1941.
7. Enzer, N., Simonson, E., and Blankstein, S. S. Fatigue of patients with circulatory insufficiency, investigated by means of fusion frequency of flicker. *Ann. Int. Med.* **16**:701-707, 1942.
8. Alder, H. F., Burkhardt, W. L., Atkinson, A. J., Krasno, L. R., and Ivy, A. C. Effect of various drugs on psychomotor performance at ground level and at simulated altitudes up to 18,000 feet in decompression chamber. Quoted by Krasno and Ivy.[3]

THE RELATION OF THE SURGEON TO HIS GOVERNMENT*

William Jason Mixter, M.D.†

BOSTON

IN discussing this subject, I am treading on perilous and debated ground as surely as though I were between the lines in Korea, but this matter is vital to us all. The relation of the surgeon to his government is an ever-changing one, and future trends should be guided by us. We know the difficulties of the problems and we should know the proper solutions. This matter is important to us and to our country, but it is essential that we always remember this: "The prime object of the medical profession is to render service to humanity; reward or financial gain is a subordinate consideration."[1]

As we consider the history of the surgeon through the centuries, we first find him as the tribal medicine man or, in Egyptian days, as the surgeon-priest. In those days he had much to do with government; indeed, he was an important part of it. Later his status became subservient to the practitioner of medicine, and he was simply the barber-surgeon. As time went on, he again became important in his own right, for on him depended the health of the armies of the world, and the world was ever at war. In recent times the surgeon has taken an ever-increasing share in protecting the health of the community, not only in the wars between his country and its enemies but also in the fight against disease and injuries in civil life. Thus, his province has come to include not only his personal relations with his patient but the less personal relation of care of patients placed under him by state action in war or peace. Added to this is the responsibility of teaching and research. These subjects have become of major importance during the last half-century, and there is danger at times that they may cause us to lose sight of our prime object, the care of the patient.

Today we find ourselves increasingly involved with government projects, partly because of the devastating wars that have so plagued the world and partly because medicine, in its widest sense, is fast becoming a prime concern of the people of our country and of their governing bodies. This interest in our activities is to the advantage of all, but in view of it we must be certain that we play our proper part. We must not stand aloof, but we should do all in our power to lead in the proper development of our relations to government in the future. Our criticism, if we have any, should be constructive and not destructive.

We all can feel the increasing demands of government in every phase of our work. Government projects for the control of surgical disease, previously considered outside the governmental sphere of activity, are becoming increasingly common. In the first quarter of this century, local or national government had little or no interest in cancer, except with regard to providing a place where the indigent patient with incurable cancer might die with as little personal suffering and as little offense to the community as possible. Today we find governmental agencies at all levels taking a lively interest in cancer in all its stages and in cancer research.

*Presented at the annual meeting of the New England Surgical Society, York Harbor, Maine, September 21, 1951.

†Member, Boards of Consultation in Neurosurgery, Massachusetts General and Beth Israel hospitals; professor of neurosurgery, emeritus, Harvard Medical School; formerly chief, Neurosurgical Service, Massachusetts General Hospital.

In research of all sorts and in teaching, government is playing an increasing role, and the pressure on our medical schools and teaching hospitals is mounting. Wherever we turn we find new uniforms in our student groups, and new government agencies fostering research in everything from basic science to the strictly surgical subject of the treatment of burns.

During World War II about a third of the doctors of this country were in uniform. With the threat of war as great as it is now, our interest in military medicine is considerable, and we should study the lessons of the past in order to be intelligent concerning future trends. Except for the Armed Forces, the agency that bids fair to increase more rapidly than any other is the Veterans Administration. This giant in our midst is caring for an increasingly larger group of the population. As the veteran ages, he needs more surgery; so do his wife and all his relatives.

These are all specialized forms of state medicine. Over all lies the cloud of the possibility of state-subsidized medicine with all its present and future difficulties and dangers.

These are our major contacts with Government, now and in the future:

The Problem of State Medicine

Will the United States follow England's lead? This aspect of the subject is too vast to discuss here. I have confidence that the people of our country are too wise and farseeing to embrace that false god. As General Hawley says, in speaking of the relation of the hospital and the community:

> Too many of our people have yet to learn that Government always takes more than it gives, that we pay an excessive price in liberty, in quality of product, and even in dollars, when we transfer to Government the responsibilities that are in essence those of the community.

Public Health

Service for the public health is continually broadening its field and is our business as much as is the health of our private patient. The problems arising from our relation to public health touch us at every turn, whether it concerns one of our patients who has been admitted to a Marine Hospital or the request that we take part in a state cancer clinic. The growth of these many agencies is, in the main, orderly, praiseworthy and worth while. If public-health activity in Government suffers a forced expansion in the attempt to use it as an entering wedge for state medicine on the British pattern, we should resist such expansion to the utmost. State medicine should stand or fall on its own merit and not be allowed to grow insidiously under the cloak of the Public Health Service.

The Armed Forces

The demand from Government at present is for large numbers of younger men for duty with troops, as ward surgeons and in various capacities in which the highest grades of surgical skill and mature judgment are not essential. Positions as surgical consultants, chiefs of service and specialists and other such posts are being filled as far as possible by officers chosen from the regular establishment. I believe this policy may lead to difficulties if an all-out war should come. There would immediately be a great expansion of professional work in the various forces, and many of the men who filled these positions in World War II would be called up again, as the regular establishments would not have enough men of proper caliber for the purpose. These older surgeons come to their tasks with little or no knowledge of the lessons of Korea. It would seen reasonable to the services to call to active duty an uncertain number of men of wide experience for service overseas and also in this country. These men should be first-class surgeons and selected with great care. In addition, the group of civilian surgical consultants should be reactivated. Most of us who served in this capacity in World War II are too old to resume the job, much as we would like to. The civilian consultant has a definite advantage over his opposite number in uniform. He can report to higher authority as he will, not through channels. There are other important advantages, also. The civilian consultant can do his military work without giving up his position as chief of service or as a teacher, thus conserving surgical manpower in the upper brackets. Civilian consultants should be used primarily in the Zone of the Interior, but occasionally they should be used overseas to effect a better liaison between the overseas theatres and the Zone of the Interior.

Plans are said to be ready for such an expansion in the group of consultants in uniform. I believe these plans should be implemented at once and that the civilian-consultant group should be activated as well. Such action would free many officers of the regular services who are not particularly well fitted for the strictly surgical positions. These men could then be used in administrative positions for which they are fitted and that are difficult to fill from civilian ranks. Such a method of choice would seem to offer the best possible care of the sick and wounded in the Armed Forces with a minimum of disruption of schools and civilian hospitals. Consultants, — and particularly civilian consultants, — should not be confined to clinical consultation. Their main function must be to work in close cooperation, — the one group with the other, — and to act as technical advisers and inspectors. They must be able and willing to evaluate the men who are doing the actual surgery, to advise concerning their fitness and, above all, to see that the proper man is picked for the job, whatever it may be. I believe it is up to the members of societies such as ours to accept such positions if offered. At present the difficulties of military service loom large and it

is the fashion to avoid like the plague the resumption of a uniform. This deplorable condition is present throughout the entire population. It should be the boast of our specialty that we serve gladly and freely, no matter what the cost. The surgeons of this country may well be proud of their record in World War I and World War II. The transition from civil practice to the life of a surgeon in the Armed Forces is no simple matter, but they solved their problems splendidly.

In time of war it is essential that surgical manpower be utilized as economically as possible. In this connection we must consider the criticism, heard both from the general public and from surgeons, concerning the apparent waste of technical and professional manpower in time of war or during mobilization in the past. Granted, there were errors, but the surgeon who grumbles because he has no surgery to perform must remember some of the difficulties. We must admit that there is wastage at times, but this is often unavoidable. The important point is to keep this wastage at an irreducible minimum. It takes months to prepare for a big strike, — particularly a landing operation, — and during all that time there are no wounded to care for. Once the battle begins, a surgeon works many hours without respite. After the battle come the difficulties and delays of transporting the troops and the surgeons home. If plans are made for a hundred thousand casualties in a few weeks, many hospitals must be established along the lines of communication, and it takes almost as long to transport them back as it did to carry them forward. We civilians, when we are thrown into such a mass movement, must accept the dicta of the few who know the plan and must accept these delays with good grace.

I believe that one of the great tragedies of World War II was the needless sacrifice of our superb war machine by too rapid and ill-timed withdrawal and demobilization.

On the other side of the picture, however, is the fact that there was, and now is, some unnecessary wastage of technical and professional manpower in the Armed Services. It is in the correction of this problem that civilian surgical consultants to the Armed Services can be most valuable. A civilian consultant, who is privileged to make his report outside "regular channels," has a position of unparalleled usefulness. He has an opportunity to correct technical errors quickly and to draw the attention of those in supreme command to the necessity of utilizing precious specialist knowledge as fully and efficiently as possible. He is also able to correct the inequities in such utilization that can be so destructive to a surgeon's morale. It should be re-emphasized that members of our society ought to be willing and eager to serve in such a capacity if called on. Let us urge to the Armed Forces the creation of the post of civilian consultant in sufficient numbers to cover anticipated emergency needs, and let us ask that such posts be filled by outstanding surgeons without delay.

Research

The role of government in research has changed tremendously during the last half century. The days when the surgeon put his hand in his own pocket or interested some philanthropic friend in his work have gone with the wind, except in rare instances. The first step in this change came with the setting up of the large philanthropic foundations. The help given by these bodies was much less personal, but it probably resulted in better work for that reason. Projects were judged on their merits, and those not worthy of assistance were turned down. Closely allied to this was the entrance of the great industrial corporations into the field of medical research, and at the same time came the great expansion of governmental interest in research. Surgeons are deeply involved in investigative work of this nature, and the field extends from the scientific schools, such as the Massachusetts Institute of Technology, through the medical schools to the evaluation of groups of cases in community hospitals. In this field we find ourselves rubbing shoulders with many other groups, even those with no apparent interest in surgery. The development of high-voltage x-ray technics is of great interest to the makers of heavy guns, in relation to the detection of flaws in their manufacture: hence, the work at Massachusetts Institute of Technology is sponsored by the gun makers as well as by groups interested in surgical lesions. It is natural that industry and Government should look critically at the results anticipated from any project they are asked to finance and that they choose those whose goal is clear cut and of interest to them. This may tend to narrow the scope of a particular research project, but, on the other hand, some aspect of the problem that is to us a side-issue may stimulate governmental or industrial interest. This trend toward governmental and industrial subsidization gives a greater impetus to research, but we must be careful that research does not crowd out the other activities of our schools and hospitals.

Hospitals are primarily for the care of the sick, and the primary purpose of medical schools is the education of more doctors. Unless the project has a special priority, we must not allow it to damage these primary functions, either by neglect or by financial embarrassment. Hospitals must watch their *per-diem* cost per patient and schools the cost of their curriculum. In the main, I think this trend toward governmental subsidization of research is healthful. We must see to it that Government receives its money's worth but that it does not take unto itself the power to dictate how our institutions shall be run. Too often government

subsidies have small strings attached to them; these strings may prove to be nearly invisible wires of great tensile strength.

In this connection we must consider the National Research Council and the various committees and boards directly under the control of the Council or interlocking with it. The Research Council is not new. It dates back, I believe, to the Civil War and was organized by Abraham Lincoln. It has retained its organization through the years, although it functioned only sporadically until World War I. At that time it was revived, and it has since played an increasingly important role in the scientific developments that have given our country world leadership in many fields. This body, as far as I can determine, is entirely free from any taint of politics or favoritism. Through its medical committee and its relations with other governmental bodies fostering medical research, it has done remarkable work, quietly and without fanfare. We should co-operate with the Council and its various committees in every way possible. When in need of advice or assistance concerning any research problem, we can consult this group with the knowledge that we will be given a fair and impartial hearing.

Teaching

This is an important function of the surgeon. Whether he be a professor in one of our schools or an assistant in a hospital under a three-year resident-training program, he is a teacher, and on him rests the responsibility of giving the surgeons of the future the best possible education. The development of these young men is mainly the concern of the medical schools and voluntary hospitals of this country.

One might say that state universities and hospitals are supported by Government. In one sense that is true, but the relation of these teaching facilities to the government of the individual state is very different from control from Washington. Much teaching is done in the Veterans Administration Hospitals and in hospitals of other government agencies, but this is almost entirely at the post-graduate level and is of small volume as compared with the programs functioning outside these institutions.

Medical education, — and in particular the education of a top-flight surgeon, — is very expensive, but so far the schools are carrying the load. Certain groups of such men are being aided by various governmental agencies, — particularly in the post-graduate field, — but their individual instruction is given by the teaching staff of the school and the surgeons of the hospital. Surgical teaching is an ill-paid field, and it is to the credit of the budding surgeon's instructors that they do their work largely for the love of it. As in research, it is up to us to co-operate with Government in every way. It is perfectly proper to accept certain subsidies for specific purposes, but it is essential to the best interest of the schools and hospitals, — and also of the hospitals' patients, — that they preserve their autonomy and individuality. For this reason I believe that blanket subsidies to these institutions would be a definite step in the wrong direction. Free enterprise in our democracy has always been a precious heritage. Freedom from governmental restriction for both teacher and student is equally precious.

The Veterans Administration

For good or ill, the Veterans Administration is part of the American scene and will be as long as any of us lives. No one questions the fact that the veteran with a service-connected disability should be given full coverage. We should, however, examine the activities of this agency, which has grown so rapidly since World War II. Immediately after the cessation of hostilities, Army hospitals were taken over and new hospitals built. Plans were made for integrating these expanded Veterans Administration facilities with medical schools and large teaching hospitals through newly organized Dean's Committees. These committees functioned in an advisory capacity in the selection of staff members and in the determination of the curricula. Leading surgeons throughout the country were placed in positions of responsibility.

It soon became apparent that the Veterans Administration would be called on to care for increasing numbers of patients suffering from ailments in no way connected with their war service, and the question of widening the coverage of the ex-service man is frequently raised. This increased use of Veterans Administration facilities has been given impetus by the fact that many of these hospitals have had empty beds.

At first it was thought that only those veterans who could not afford the cost of illness would be treated for non-service-connected disabilities, but that rule has never been enforced. The trend has been to build more hospitals, to care for more patients and even to disregard the plan of building these institutions in the vicinity of our teaching centers. These are, of course, good hospitals, — well staffed, — and the best of care is given the patient. For certain groups of cases there are few civilian hospitals that can provide treatment approaching that given by the Veterans Administration. The care and rehabilitation of the paraplegic is a shining example.

If the medical care of the veteran and his family becomes a function of the Veterans Administration, then we immediately have State medicine for a privileged group in our midst. How far should this trend be allowed to go?

If the Veterans Administration is in a position to give the ex-service man better care than can the

civilian hospitals in his vicinity, let us by all means give him these advantages for any type of disease, service-connected or not. If he is unable to afford civilian care for a non-service-connected disability, let him be cared for by the Veterans Administration, but let us be sure that he really is unable to pay his way. There is no reason that coverage should be extended to include his family.

There is danger, due in part to the great size and importance of the Veterans Administration, that medical policies may be dictated by nonmedical persons whose knowledge of the problems involved is inadequate. An easy transition from such a policy might be manifested, for instance, by the discarding of the merit system and the making of appointments on the bases of seniority and favoritism.

I hope not to be misunderstood. I have nothing but admiration for the devoted men who have entered this service in order to give the veteran the best possible surgical care. In the hospitals with which I am familiar the treatment is superb. This high level of service must be maintained. If the Veterans Administration becomes a political football and professional care deteriorates, then Heaven help the disabled veteran. We must do all in our power to prevent this disaster.

I have discussed several phases of our contact with Government. Our own duties in these matters must also be summed up. First and foremost, we must view any new trend with a critical eye. We must measure such a trend on a simple yardstick — Is it good for the patient? If these future trends do not qualify, they should be resisted. Any surgeon connected in a civilian capacity with governmental hospitals must be careful that our interest in our professional work does not carry us too far. It is all too easy to forget that these men and women are patients and that our duty is to them. We must not use our privilege to build up a good series of cases for ourselves or to use patients for teaching purposes to their detriment. Whether we are full-time or part-time in any government hospital, we must always keep this obligation in mind.

I should like to reiterate at this point some of our own more general obligations to the Government. Too often we refuse to serve unless drafted for service. Too often we refuse to adapt ourselves with good grace to the exigencies of government service. Too often we refuse to guide public opinion with constructive rather than destructive criticism.

We surgeons, if we are worth our salt, are respected members of society. We are looked up to, and our opinions carry weight. We must be sure that we retain that respect. To that end let us co-operate in every possible way with these Government agencies of ours. Wherever possible, let us help in their work.

Finally, what stake has the public in our success and in our relations with the Government? It is a large stake, for on our success and contentment in our profession depends the caliber of the men who will follow us in our exacting vocation. On the intelligence and technical skill of these men will depend the well-being of everyone who is placed on an operating table. If we are unhappy in our work, if we cannot teach these young men successfully, if we are regimented and if our freedom of thought and action are restrained, our successors will think twice before they take up our tools.

The surgeon of today and tomorrow should be able to make a decent living, yes — but above and beyond this, if he is worthy to succeed to the standards of New England surgery he must labor for eminence in his profession, respect in his community and work well done for humanity.

We, the surgeons of today, must see to it, for the benefit of the patient of tomorrow, that the staff of Aesculapius is ever the symbol of progress and freedom.

References

1. *Principles of Medical Ethics of the American Medical Association.* 28 pp. Chicago: American Medical Association, 1938.
2. Hawley, P. R. Medicine as social instrument: hospital and community. *New Eng. J. Med.* **244**:256-259, 1951.

MEDICAL PROGRESS

DISEASES OF THE THYROID GLAND (Part I, Concluded)

OLIVER COPE, M.D.*

BOSTON

HYPERTHYROIDISM

A revolution in the treatment of hyperthyroidism has taken place during the past ten years. In the eighteen years prior to 1941 the treatment of hyperthyroidism had become the province of the surgeon. Today hyperthyroidism can be treated successfully by any one of three therapies, two medical and one surgical. The initiation in 1941 of radioactive-iodine therapy has raised the radiation treatment of this disease from a sporadically successful to a predictable therapy. The introduction of the thiouracil compounds in 1943 has provided a second medical therapy; many consider it as efficacious as radioactive-iodine treatment. Its use in preoperative preparation has also increased the success of the surgical management to the degree that crisis, mortality and technical complications are virtually eliminated. Which treatment is best?

Treatment Prior to 1941

Prior to 1941 the indifferent success of nonsurgical therapies of hyperthyroidism left surgery as the dominant method. Because of the early mortality and continued complications of operation, however, medical therapies were hopefully tried, one after another.

One of these medical therapies, which received little attention outside southern Germany and is now of historic interest because of the successful use of the thiouracil drugs, was the custom of sending patients with exophthalmic goiter into the mountains for a two-year sojourn. These mountains were the seat of endemic, iodine-deficient goiter; in retrospect, what the therapy accomplished was to deprive the patients of iodine. It is, therefore, a therapy akin to the current chemical deprivation by the thiouracil compounds. The therapy was practiced as late as 1926 by Friedrich von Müller, who, it will be recalled, was the Munich professor of medicine who first described the negative nitrogen balance of patients with hyperthyroidism. This therapy was, of course, uneconomic. It was also uncertain, since the disease failed to burn out in many patients in two years.

X-ray was also widely tried; in certain clinics it was used continuously for many years. The relief rate varied, recovery was slow and uncertain and the method was considered unpredictable.

Iodine was the only important drug therapy of this period. It had been recommended in the treatment of hyperthyroidism by Trousseau in the last century with reported success but had been generally avoided because of the fear of causing acute hyperthyroidism in patients with iodine-deficient goiters, the so-called Iod-Basedow disease. In 1923 Plummer, of the Mayo Clinic, reintroduced it and demonstrated its usefulness. It was found, except in those few patients whose goiters were already replete with iodine, to bring about amelioration of the hyperthyroidism. How this takes place is still a matter of conjecture.[71, 72] Anatomically, the administration of iodine resulted in a reduction of the hyperplasia — that is, a decrease in the papillary infoldings and in the number of mitotic figures, a storage of colloid and a decrease in the vascularity of the gland. There may or may not be a decrease in the lymphoid hyperplasia. Anatomically, therefore, a reversal of the disease process associated with hyperthyroidism takes place.

In physiologic association with the storage of colloid in the gland, a decreased secretion and a drop in the metabolic rate were noted. In patients with a severe degree of the disease the severity was lessened. It was only in mildly affected patients that iodine was observed to relieve the overactivity. It was therefore in only occasional cases that iodine proved a satisfactory long-term medical therapy.

Iodine proved, however, to be a boon to surgical therapy. The great hazards of surgery were connected with severe cases. Anesthesia and operation tended to promote crisis. The iodine-induced remission greatly reduced the incidence of crisis, surgical mortality and surgical accidents in general. With the introduction of iodine came general improvement in the care of the patient, including more care in nutrition, and with it the surgery of hyperthyroidism changed from a hazardous procedure to a well organized surgical accomplishment. By 1941 mortality and complication rates were reduced from the almost prohibitive level of 1923 to an acceptably low level. It was necessary, therefore, that any new treatment introduced as the sole medical therapy replacing the surgical method should have an equally high degree of success.

Treatment After 1941

Radioactive iodine. The use of radioactive iodine offered the possibility of such success. With the development of the radioactive isotopes of iodine their use was logically indicated for the treatment of hyperthyroidism.[73, 74] Iodine is an integral part of the thyroid hormone, and no other gland or tissue of the body absorbs and holds this element in appreciable concentrations. After iodine is given to an animal, either by mouth or injection, that part not absorbed by the thyroid gland is

*Associate professor of surgery, Harvard Medical School; visiting surgeon, Massachusetts General Hospital.

promptly excreted through the kidney. The radioactive isotopes of iodine give off an intense radiation. When given to a patient they should deliver the radiation to the very cells that are manufacturing the excess of hormone. Where the skin had limited the dose of external irradiation that could be given to the gland, it was believed that enough radiation could be given by the use of radioactive iodine to reduce the number of the offending cells to the extent of relieving the hyperthyroidism.

This theoretical concept was proved valid in practice. The first patients were treated independently and virtually simultaneously in 1941 — at the Massachusetts General Hospital by Hertz and Roberts[73] and in San Francisco by Hamilton and Lawrence.[74] Many patients have now been treated by this method.[75-81]

The mode of action of radioactive iodine in relieving hyperthyroidism is physiologically simple. The thyroid cell needs iodine to produce its specific hormone. The cells of the hyperthyroid goiter are abnormally avid for iodine, and if they have not recently been surfeited by large doses of inorganic iodine these cells seize on the dose of iodine that contains the radioactive isotope. Since a high titer of radiation is contained in a minute dose of inorganic iodine, an almost unlimited dose of irradiation can be delivered to the overactive thyroid cells. A dose can be delivered that actually necroses the cell that absorbs it. The effect of the isotope is brought about by a high-energy beta radiation with a relatively short penetration (not over 2 to 3 mm.). The zone of radiation effect is therefore limited.

Grossly, the effect of the treatment is to shrink the hyperplastic goiter to a thyroid gland approximately normal in size. The microscopical sections suggest that the total amount of secreting thyroid epithelium is reduced. The effect of the irradiation, therefore, is in essence a subtotal thyroidectomy. Surgical biopsies of treated glands taken during the first three days after the initiation of irradiation therapy show acute necrosis of the thyroid cells, with edema throughout. The biopsies made in the later phases show healing with fibrosis. By the third and fourth months the residual thyroid epithelium is intensely hyperplastic. Surgical resection of residual goiters performed one to three years after irradiation shows that the dense fibrosis and intense hyperplasia of the thyroid epithelium persist.[65] Whether this persisting hyperplasia of the remnant is due to the fact that the total amount of thyroid epithelium is reduced and hyperplasia is needed to meet the normal hormone requirement or whether it is a continuation of the pretreatment stimulus of the Graves' disease is not known.

The radioactive iodine may be given in single or divided doses; clinics differ in their preference. When it is desired to apply all the radioactivity in one dose the dosage is calculated on the basis of the estimated size of the goiter and the degree of toxicity.[76] The divided doses may be repeated until the desired effect is obtained.[82] The single dose has the advantage of more prompt relief, but if an excess is given, hypothyroidism results. By the divided-dose technic hypothyroidism is more easily avoided. Goiters vary in their sensitivity to irradiation; the more hyperplastic are the more sensitive. Nodular goiters are so resistant that some physicians prefer other forms of treatment in order to avoid the heavy doses of irradiation required to bring about a complete remission.[80]

The radioactive-iodine treatment is highly successful. Approximately seven weeks are required before the full effect of the irradiation is apparent. A short latent period commonly precedes the drop in metabolic rate. A mild exacerbation is sometimes seen during the first few days.[78] When the multiple-dose method of treatment is employed, six to eight weeks should intervene between each dose; otherwise, hypothyroidism may result.

Because of the long latent period between irradiation and relief, some clinics prefer to initiate treatment of the hyperthyroidism with propylthiouracil or another of the thio- compounds.[65] When the hyperthyroidism is in abeyance the thio- compound is withdrawn, and after forty-eight hours the dose of irradiation is given. The irradiation prevents the production of thyroxin before a post-thiouracil exacerbation can occur. This combined use of a thio- compound and radioactive-iodine irradiation results in a more prompt relief, but it does not necessarily aid in the estimation of the dosage of irradiation needed for final relief.

Relief from thyrotoxicosis is complete if a sufficient dose of radioactive iodine is given. If there is residual thyrotoxicosis the dosage of irradiation was inadequate and more should be given. In order to avoid an unnecessary hypothyroidism it is perhaps wiser to start with a conservative dose, using the single-dose formula, and accept the necessity of a second smaller dose should thyrotoxicosis persist.

Insufficient time has elapsed for us to know the true recurrence rate. Some of the recurrences reported after radioactive-iodine irradiation may represent residual hyperthyroidism. Certainly on the evidence available the recurrence rate is as low as that following surgical subtotal thyroidectomy, and it may prove to be lower. The intense fibrous scarring caused by the irradiation may ultimately prove to prevent the regrowth of goiter that sometimes occurs after subtotal thyroidectomy. No such regrowth has as yet been reported as following irradiation.

The radioactive-iodine-radiation therapy of hyperthyroidism is noteworthy for the virtual absence of significant early complications. The sore throat, with hoarseness and a tender goiter, that followed the early therapy with the short-half-lived isotope

has already been alluded to. These irradiation effects are clinically less significant when therapy is carried out with the eight-day-half-life isotope; with this isotope the major portion of the irradiation is spread over a period of ten to fifteen days.

The immediate exacerbation of the hyperthyroidism in the days following the onset of irradiation has thus far not led to complications. It has been mild when encountered at the Massachusetts General Hospital. Werner, Quimby and Schmidt observed it in 3 patients, and the rise in metabolism was only 15 per cent.[78] The exacerbation is believed to be due to an unloading of the thyroid hormone stored in the gland prior to the irradiation. With the radiation necrosis and edema, this hormone is believed to be washed suddenly into the general circulation during resorption of the edema. The possibility that this exacerbation might be severe enough to lead to crisis in the severely toxic patient must be admitted. Such an exacerbation of hyperthyroidism has been well documented in a patient with a thyroid cancer and functioning metastases.[83, 84] In this case the treatment with radioactive iodine released the hormone from the metastases. The exacerbation is a second reason for starting the therapy with propylthiouracil and withholding the radioactive iodine until the hyperthyroidism is in at least partial remission.

The tetany of hypoparathyroidism has not been reported. It was natural to believe that the parathyroid glands might suffer from irradiation, and hypocalcemia has been looked for.[65] The parathyroid glands usually lie close to the thyroid capsule. Sometimes they are imbedded in a thyroid sulcus and would thus be irradiated on all sides from the thyroid gland. Either the degree of penetration of the irradiation is not great enough to reach the parathyroid glands in sufficient quantity or the normal parathyroid glands are too resistant to irradiation to be disturbed, as the calcium levels of the patients tested have remained normal.

The possibility has been suggested that the heavy radioactive-iodine irradiation needed to relieve the hyperthyroidism will eventually result in a malignant degeneration of the thyroid gland or of its neighboring organs.[85-87] This possibility is hotly contested; some believe that there is no reason to fear a carcinogenic effect.[85, 75] Unfortunately, no data bearing directly on the issue are as yet available. Which side one takes depends upon personal experience. Few workers believe that they know enough to express an opinion in writing. Such hesitation is praiseworthy in the event that the fear of carcinogenesis proves to be groundless. It will have been negligent if carcinoma ultimately develops. As responsible clinicians we cannot avoid the issue and must find a position. What is the evidence?

Carcinoma may be a late complication of irradiation in a variety of tissues.[88-90] Malignancy may develop in areas of skin that have been treated by heavy doses of irradiation given to destroy benign lesions.[91] Evans has made a survey of patients with such benign lesions treated at the Huntington Hospital twenty-five to thirty years ago who are known to have subsequently developed cancer in the irradiated area.[92] The gamma radiation of radium had been used, and although the roentgen unit had not been developed at that time he was able to calculate the dosage from the full details of treatment given in each record. In no case had the irradiation been given in a single dose; the treatment had been applied in multiple doses spread over a period of years. The total dosage was very high — in the neighborhood of 100,000 r. The malignant degeneration had taken fifteen or more years to develop. The inference drawn by Evans is that malignancy develops only as the result of chronic, repeated insult.

Evans' survey suggests that there might be danger in treating the thyroid gland with repeated doses of radioactive iodine over a period of years. His survey does not say what might happen if one tenth of that high dose were given in a single application or in a few applications within a short period. This is, however, our problem with the thyroid gland. His study did not include a review of the dosage in patients not developing malignancy. The top dosage given to patients in a single dose is therefore not known. It is unlikely that during that period at the Huntington Hospital amounts even approximating 10,000 r were given to skin in a single application or in divided doses within six weeks.

In view of the hazard of excessive irradiation of skin, the Tumor Clinic of the Massachusetts General Hospital has a long-standing rule that no benign lesion of the skin of a younger person may be treated by more than an erythema dose of irradiation, from either x-ray or radium. The radiologists of this Tumor Clinic have repeatedly called to the attention of the Thyroid Clinic the hazards of too large a dose of irradiation from radioactive iodine.[87] One thing that has been learned from our experience with lesions of the skin is that in point of time we may not have our answer until another ten to fifteen years have passed.

Brues, of the Argonne National Laboratories at the University of Chicago, has discussed the possibility of carcinogenesis as follows:[86]

> In treatment of thyrotoxicosis, I^{131} has been used in relatively high thyroid dosage by a number of clinical groups. . . . Dosages of 200 or more microcuries per gram of thyroid are frequently used, with a resultant total radiation dose in excess of 10,000 rep. The actual dose has been estimated to be as much as 26,000 rep with 200 $\mu c/g.$,[93] but is difficult to estimate, since it depends on the rate of loss of iodine from the treated gland. If the dose to the tissues immediately surrounding the thyroid is one-half to one-fourth of this, it appears that the adjacent connective tissue receives thousands of rep. This is in the range of dosage by x-ray which has resulted

in bone tumors in man,[88] and it will be recalled that 3,000 rep of external beta radiation to rats from P^{32} has resulted not only in epitheliomas, but in subcutaneous sarcomas as well.[94] It is, therefore, within the bounds of possibility that carcinogenic effects may occur from dosages as used in the treatment of thyrotoxicosis, although it is encouraging to note that no reports of such sequelae have appeared after several years' clinical experience.

In a personal communication Brues suggests that sarcoma developing in the thyroid capsule or in adjacent organs of fibrous-tissue origin is as much to be feared as carcinoma in the epithelial cells of the thyroid gland.

Nickson, speaking on the basis of his experience at the Sloan–Kettering Institute and the Royal Cancer Hospital in London, also tries to grapple with this elusive subject.[85] He recognizes the hazard but does not know the safe dosage. He writes:

> The use of radioiodine in the treatment of non-malignant diseases of the thyroid should be reserved for those persons in whom the other possible means of therapy have failed, or cannot be used. If all our therapeutic attempts are limited to these classes of patients we can never fairly be charged with irresponsible or heedless use of a potentially dangerous material.

Nickson's position is exemplary, but it must be admitted that if we follow his advice very few patients will be treated, and an adequate answer to the question of whether the treatment is hazardous may be postponed for a generation. A most valuable therapy might be needlessly withheld.

Quimby and Werner have sought an answer by finding out whether carcinoma has developed in the goiters of any patients whose hyperthyroidism was treated by external x-ray irradiation.[95] They sent a questionnaire to radiologists and clinicians who had been treating hyperthyroidism by x-ray. Fifty-three radiologists and 18 clinicians responded. They listed 10 cases of carcinoma, but apparently the radiation could have been responsible in only 3. Quimby and Werner concluded:

> It appears that the possibility of late malignant degeneration is negligible following roentgen therapy for toxic goiter. It may be presumed that the hazard is not much greater for radioactive iodine therapy, but this cannot be verified for a number of years. Only a long term follow-up of an extensive series of cases will finally determine the safety or danger of this procedure. Accordingly, for some years at least, everyone employing this method should make all possible efforts to follow cases persistently. In the meantime the material should not be used indiscriminately. Reasonable criteria should be established for the selection of patients, and dosage levels should be based on careful calculations.[95]

It is clear that their conclusion concerning external irradiation is justified. As regards internal irradiation by radioactive iodine, any conclusion must take into account the fact that the dose of external irradiation was limited by the need of avoiding skin damage, whereas the radioactive-iodine irradiation is many times as great. It is possible, perhaps probable, that the risk of late carcinogenesis is proportionate to the dose.

The opinion of the pathologist has been sought. He, too, is limited by tools that do not permit him to take a definite position. He can at best offer only a tentative opinion. Pieces of the goiters of patients have been obtained by surgical biopsy or resection from days to six years after the radioactive-iodine treatment.[65] One patient was murdered eight years after such treatment and the thyroid gland was obtained at autopsy. Microscopical sections of these pieces have been reviewed by a number of pathologists, who agree that there is scarring and continued hyperplasia. The majority do not recognize any definite untoward changes. Stewart, of the Memorial Hospital in New York, has recently reviewed some of these sections; in those taken six and eight years after irradiation he sees the abnormal configurations of the nuclei that he associates with premalignant changes following irradiation in other tissues. He thinks that the future of such glands is unpredictable but possibly ominous.[96]

A final disadvantage of radioactive-iodine therapy is the expense to the physicians and institution administering it.[77] The physician must have acquired training in the use of isotopes. Advice from the radiologist is needed. The help of a physicist is required for proper maintenance of the apparatus. Finally, the institution must invest much money in apparatus.

The indications for radioactive-iodine therapy of hyperthyroidism are tempered by the physician's opinion concerning the hazard of late carcinogenesis. It is obvious that some physicians give this therapy with no hesitation. Others hesitate to the extent of advising against its use.

The disadvantage of possible late carcinogenesis must be weighed against the advantages of the treatment, which are substantial. For the patient it is the simplest and least expensive method. Hospitalization is usually unnecessary, the patient being cared for as an out-patient from start to finish. After the diagnostic work-up and the radioactive-tracer test for calculation of the dosage, the indicated dose is given in a small drink and the patient returns home to await the outcome. The apprehension, discomfort and expense of operation are obviated, and the result is certain.

The considered opinion of the Massachusetts General Hospital Thyroid Clinic, a consensus of opinion among internists, surgeons, psychiatrist, pathologist and biophysicist is as follows:

The radioactive iodine therapy of hyperthyroidism is controllable, predictable and successful. Its principal disadvantage is the possible hazard of late carcinogenesis. What this hazard is, is not known. The facts essential for critical decision are not as yet available. The therapy is, therefore, to be reserved for patients in whom late carcinogenesis will not become a question or in whom the disad-

vantages of another therapy outweigh the possibility of late carcinogenesis.

It is the therapy of choice in any patient whose life expectancy is not over twenty-five years. It is thus the therapy in the patients of the older age group or in those who have a coexistent other disease that may limit the life expectancy.

It is not necessarily the treatment of choice in patients with toxic nodular goiter — and for three reasons. First, the incidence of carcinoma is significantly higher in nodular goiter. In such patients care must be taken to exclude the presence of carcinoma. If carcinoma cannot be excluded on clinical grounds, the operative approach is the treatment of choice. Secondly, the dosage required may be higher, repeated doses are more likely to be needed and the time span for relief is prolonged. Thirdly, the goiter is less likely to resolve and nodules are more likely to persist. Such nodules may require surgical excision in any event.

Radioactive iodine is the treatment of choice in a patient of any age who has a recurrence of hyperthyroidism after one or more previous thyroidectomies. It is preferable in this instance to prolonged drug therapy, since the disease is already recurrent and drug therapy may be even less likely to effect a permanent cure.

It may be the preferred therapy in patients expected to have a poor psychologic reaction to therapy — patients in whom the anticipated reaction to surgery will be worse.

A criterion for therapy in all patients is that they be available for long-term follow-up and that they be able to co-operate in the follow-up program without anxiety being aroused. It is the responsibility of the clinic to follow all patients through the twenty-five-year period until the problem of the late hazard of the irradiation has been eliminated or determined.

The Thiouracil Compounds

A new epoch in the treatment of hyperthyroidism dawned in 1943 when Astwood introduced the thiouracil compounds.[97] These drugs, as has been previously mentioned, chemically block the elaboration of iodine into the specific hormone, thus preventing hormone production. Accompanying this blocking there is an intensification of the thyroid-stimulating action of the anterior pituitary on the thyroid cells.[98] The normal gland of a normal person or animal given one of these drugs becomes hyperplastic. The hyperplastic gland of a patient with Graves' disease develops an intensification of all the aspects of the hyperplasia.[99] There is an increase in the number of mitotic figures and in the papillary infoldings, further disappearance of colloid, more lymphoid hyperplasia and greater vascularity. The anatomic effect of these drugs on the thyroid is therefore exactly the opposite of that of iodine. When iodine is given in addition to the thiouracil drug it still has an involuting effect — that is, the iodine is able to temper the hyperplastic effect of the thiouracil.[71]

The thiouracil drugs are rapidly excreted, and in order to maintain a sufficient concentration of the drug within the thyroid gland to block the iodine synthesis it is necessary to give the drug in sufficient quantity and at eight-hour intervals. If only one dose is given in a day the level may fall low enough prior to the next dose to induce production of the hormone. This matter of staging the doses is obviously of great importance when iodine is being given simultaneously and the cells contain a higher than normal concentration of iodine.

The gross effect on the goiter is a softening and an increase in vascularity. If no thrill is present initially it may be noted after ten days of therapy. The softening is believed to be due to the resorption of colloid and to increasing vascularity. The size of the goiter depends upon the interrelations of stored colloid, the number of cells and the vascularity. When involution of a hyperplastic gland is induced by iodine, with the storage of colloid the gland ordinarily increases somewhat in size. This increase is tempered by the accompanying decrease in vascularity. When thiouracil alone is given, the resorption of colloid may be offset by the increase in vascularity with no concomitant change in the size. The softness of the gland leads many patients and physicians to believe that the gland is smaller than it is; at operation the surgeon may be surprised at its actual size.

The speed of action of the thiouracil drug on the level of hyperthyroidism appears to depend on the state of the goiter prior to initiation of therapy. If the goiter consists only of intense hyperplasia with little stored colloid, the metabolic rate drops promptly. The metabolic rate may fall to normal in three weeks. If the goiter is well involuted, with a large quantity of stored colloid, there may be a long latent period of drug therapy with no drop in the metabolic rate.[100] In some cases the metabolic rate begins to fall only after three or four months have passed.[99] Once the fall begins, it generally proceeds rapidly. There is no proved case of hyperthyroidism in which the goiter has not eventually responded with an ultimately normal metabolic rate, provided that the drug is given regularly, persistently and in a large enough dose.

It is possible to control the thyroid function at almost any level by varying the dosage of the drug. It is the usual practice to employ a relatively large dosage at the onset of therapy to ensure a prompt effect. If this dosage is continued after a normal metabolic rate has been reached the function will generally be reduced to a subnormal level. Myxedema can be induced. It is therefore the usual practice to reduce the dosage when a normal metabolic rate has been reached, tapering off to the smallest quantity adequate for maintaining

a normal level in that patient.[100, 101] The actual dosage used varies among the types of the drug; these various types will be discussed under "Complications."

A difference of opinion exists concerning whether the simultaneous administration of iodine slows the responsive curve to the thiouracil. Bartels favors the addition of iodine from the beginning of therapy.[102] The variation from case to case is so great, even on the thiouracil drug alone, that it is difficult to be sure whether or not iodine alters the thiouracil effect; some physicians believe that it does.[65, 103] Differences in opinion may have resulted from differences in use of the two drugs.

In contrast to the prompt and complete control of the hyperthyroidism that is assured by the use of the thiouracil drugs, the recurrence rate following withdrawal of the drugs is unsatisfactorily high. If the drug is stopped as soon as a normal metabolic rate is reached, there is a prompt recurrence of hyperthyroidism in nearly every case.[100, 103-105] If the dosage of the drug is tapered off slowly, with a maintenance dose sufficient to keep the metabolic rate at or near normal for six to fifteen months, from 50 to 70 per cent of patients will have no further hyperthyroidism. Increasing the duration of the maintenance dose to two years or even longer apparently does not increase the number of cases permanently relieved. It has now been reported from several clinics in different parts of the world that when the thiouracil drugs are used as the sole therapy 30 to 50 per cent of patients will sooner or later have a full recurrence of the disease.[106-108]

Various suggestions have been made for increasing the success of this therapy. Some workers have thought that the drug therapy must be pushed to complete control and even to some hypothyroidism[102]; others believe that hypothyroidism should be avoided, since this intensifies the anterior-pituitary activity and recurrence is more likely.[107] It seems that the physician's attention to possible social and psychologic readjustments and the ability of the patient to make such adjustments concomitantly with the drug therapy might be of some importance.

Morgans and Trotter have made the most provocative analysis of exacerbations of hyperthyroidism in patients who have been treated by the thiouracil drugs.[106] Colleagues of Himsworth at the University College Hospital in London, their experience goes back to 1943 and is one of the longest and most extensive in the use of the thiouracil compounds. They watched 122 patients from 1945 to 1949 during their treatment with methylthiouracil, recording the season of the year when exacerbations and recurrences took place. Sixty-three patients showed one or more exacerbations during therapy that were sufficient to require an increase in dosage of the drug. The exacerbations were commonest in the early spring and least frequent in the fall. It was also found that drug therapy had most often been discontinued in the month of September. The distribution of season of onset of exacerbations correlated closely with the seasonal variation in daylight, suggesting that the anterior-pituitary–thyroid axis has a seasonal activity influenced by length of daylight comparable to that of egg-laying hens, birds and trout.[109]

In summary, it must be said that the reason for such a high recurrence rate is not known; as a corollary, why so many remain healthy is not understood.

When Astwood first introduced the drugs, only two were available, thiourea and thiouracil. Thiourea had an unpleasant taste; therefore thiouracil was the more commonly used. The latter had, however, a most undesirable toxicity. This aspect was reviewed in the last Medical Progress published in 1946. Fever, rashes, purpura, the Mikulicz syndrome, leukopenia and, worst of all, agranulocytosis were all too frequent; constant observation was necessary during treatment.

A masterly job has been done, largely by Astwood and his collaborators, in discovering new compounds with less toxicity.[110] Three drugs are now in fairly general use — methylthiouracil, mercaptoimidazole and propylthiouracil. The last seems to have the lowest toxicity of any drug yet found and has been given the widest trial. A certain few patients develop a sensitivity to this drug, in the form of a rash or febrile reaction, which usually disappears when the therapy is pressed. Leukopenia occurs, but agranulocytosis has been almost unknown; purpura is occasionally seen. Propylthiouracil is so effective in practice and is so free of toxicity that if the patient is available to the physician and is warned to report any rash, fever or sore throat, there is virtually no danger.[103]

The effectiveness per milligram of these drugs on hyperthyroidism varies widely. The toxicity is not proportionate in all cases to the weight of the drug needed.

Recently two iodinated thiouracil compounds have been synthesized[111]; on preliminary clinical testing they have been reported to be of low toxicity.[112-114] Experimental data have been obtained[115] suggesting that the chemical combination has less goitrogenic action for an equal antithyroid block than separately administered iodine and thiouracil. The clinical testing thus far reported gives no proof of such an advantage, although from a practical point of view the combined drug should simplify clinical management. The combined drug would also tend to ensure against unnecessarily intense hyperplasia — a theoretical advantage in prolonged drug therapy when possible carcinogenesis is considered.

Malignant degeneration has been suggested as a possible complication of the thio-compound therapy.[116-118] Certainly all these compounds induce an intense cellular hyperplasia, and the physician

familiar with malignant disease is suspicious of any hyperplastic influence. The many examples seen in various tissues and organs of the body of a prolonged stimulus to hyperplasia resulting in benign and malignant neoplasia do not permit the ignoring of this aspect.

The possibility that the thiouracil compounds might induce neoplasia through its hyperplastic stimulus was promptly investigated experimentally. As early as 1944 Bielschowsky reported the appearance of neoplasms in the thyroid glands of rats given both allylthiourea and a known carcinogen.[116] Since that time the production of both benign and malignant neoplasms has been reported by a number of workers, and there can be little question that the increased TSH activity induced by the thio drugs is responsible. (These experiments will be discussed in detail under "Tumors.")

The experience gained in experimental tumor production in the rat and mouse is not necessarily directly transferable, of course, to the problem in the human being. These experiments do suggest, however, that if an intense hyperplasia is induced for a long period tumors will result, even including an occasional carcinoma. When prolonged therapy is decided on, the minimal amount of the drug should be used. Iodine should perhaps be used more frequently to temper the intensity of the hyperplasia. The chemically iodinated compound might have an advantage and should be studied further from this point of view.

A few cases have been reported in which a carcinoma has been found in the goiter of a patient who had previously been treated with a thiouracil compound. The inference has been drawn that the thiouracil was an etiologic factor. Before this inference can be accepted it is necessary to be sure that the carcinoma has not started prior to the drug therapy. Carcinoma of the thyroid gland does occur spontaneously in patients with Graves' disease, in 0.5 to 1.0 per cent of cases (see "Tumors"). In the first such case reported it seems reasonable to conclude that the carcinoma antedated the drug therapy.[117] The thiouracil had been administered for only thirty-four days, the carcinoma was of a papillary type (these ordinarily grow slowly) and calcification was apparent in one area, an indication of longevity.

It must be admitted that in a patient in whom some other carcinogenic activity is present the thiouracil drug might tip the balance in favor of carcinogenesis. Certainly in any patient who is receiving the drug over a period of years this possible complication must be kept in mind. An undue increase in the size of the goiter, particularly if the increase is localized to one area, should be an indication for surgical exploration.

Finally, if carcinoma ever becomes a complication of thiouracil therapy, it is statistically almost negligible. The drugs have been widely used, and no increase in incidence is as yet apparent.

The thiouracil compounds offer three principal advantages in the therapy of thyrotoxicosis. From the short-range point of view, they permit the most prompt control of the excessive thyroid activity that has yet been obtained. They have virtually eliminated crisis, the most dreaded component of the disease. Used as the sole therapy of the disease they have the advantage of obviating the necessity of operation — an advantage they have in common with radioactive-iodine therapy. Finally, no complicated apparatus or special training is needed.

The disadvantages of the therapy from the long-range point of view are the protracted medical attention required and the high recurrence rate. Drug toxicity should no longer be counted as a disadvantage, and sufficient experience has already been obtained to remove the fear of carcinogenesis as a clinically significant possibility, provided that therapy is not prolonged unduly. The presence of cancer must be excluded in each goiter and at all stages of therapy, before, during and after the thiouracil therapy. (This aspect will be discussed under "Tumors.")

Surgery

The surgical treatment of hyperthyroidism has also made strides since the advent of the thiouracil drugs. Early introduced in the preoperative preparation of the patient, they have become the standard initial therapy. A thiouracil compound, now most commonly propylthiouracil, is given in full dosage until the metabolic rate is normal. Either when the metabolic rate has descended to normal or at some time in its period of descent, iodine is added to involute the gland and reduce the increased vascularity caused by the thiouracil compound. During this period of control of the hyperthyroidism, the patient may be treated as an out-patient.[71, 99, 119-121]

The control now obtainable with the thiouracil drug has removed the urgent necessity of surgical intervention in hyperthyroidism. It is not necessary to carry out the operation as soon as the metabolic rate is normal. There is no danger of an exacerbation of the disease comparable to that sometimes noted during the course of iodine therapy. There is much evidence that the patient's general condition improves during the first weeks after the metabolic rate has been returned to normal. The autonomic-nervous-system imbalance is restored to equilibrium, the patient's confidence returns and his nutritional state improves.

The patient is brought to the operating room a normal person instead of an excited, overactive, unbalanced, exhausted patient. No haste in administering the anesthetic or carrying out the operation is necessary. The operation can be performed with all the care needed to examine the problem

of the goiter, to exclude the presence of a carcinoma if nodules are present, to carry out an adequate excision if a carcinoma should exist and in any case to carry out a sufficiently radical subtotal excision to ensure relief of the hyperthyroidism and diminish the chance of recurrence. Precautions can also be observed that will virtually eliminate the hazards of postoperative hemorrhage, vocal-cord palsy and parathyroid damage. Thus, by proper preoperative care and management of operation crisis, mortality and complications should be eliminated.

The disadvantages of an operation are obvious. Surgery presents a psychologic hazard; it is disagreeable at best, and no matter how carefully it is carried out there is always the chance of human error, accident or complication. Operation is also expensive, and it is an economic waste if a less expensive method is as good.

The advantages of the operative care of hyperthyroidism are that the pathologic nature of the goiter is established. Two conditions require special attention — the hyperfunctioning single adenoma and carcinoma. Both are best handled by the surgeon. The single adenoma is excised, leaving undiseased tissue intact and undamaged.[32] In those rare cases in which carcinoma is found associated with the hyperplasia, the carcinoma can be eliminated before it is allowed to progress to an incurable state. This advantage may seem small when it is considered that hyperfunctioning single adenomas are the unusual pathologic type producing hyperthyroidism and that cancer occurs in only about 0.5 per cent of the diffusely hyperplastic goiters of Graves' disease and in 1 per cent of toxic nodular goiters.[122, 123] However, both must be recognized in the interests of proper therapy.

Another advantage of operation is that when preceded by thiouracil therapy it brings prompter relief than that from radioactive iodine. It eliminates the repeated visits to the physician required by prolonged drug therapy.

The goiter is eliminated by surgery. With continued drug therapy it may diminish, remain unchanged or even increase in size. With radioactive iodine the goiter also diminishes, but the unknown hazard of carcinogenesis remains; here lies another advantage of surgery. There is no carcinogenic action from operative excision of the goiter.

Comparison of Therapies

As these three methods of therapy, radioactive iodine, prolonged drug treatment and surgical extirpation, are compared, the following conclusions emerge. Both radioactive iodine and the drug therapy have the advantage of being medical procedures and surely it can be admitted that when two therapies are equally good, one being medical and the other surgical, the nonsurgical one is to be preferred. Radioactive-iodine therapy is by all odds the simplest method for the patient. It is as controllable and as successful as surgery. As a disadvantage, it has the hazards of the unknown. The type of goiter is not established during this treatment, and if nodules persist after treatment an operation may still be necessary. The possibility of late carcinogenesis is also unknown. Were it not for these unknown factors, this therapy would supplant the other two.

The drug therapy is also simple, but the recurrence rate after its use is too high for it to be considered truly satisfactory. It gives an excellent result so long as the patient is under observation. For practical purposes it is devoid of complications. The theoretical danger that the stimulus to hyperplasia that it induces in the thyroid epithelium might lead to carcinoma has not materialized. The danger is certainly no greater than that of complications from operation.

Surgery brings prompt relief, and its cure rate is still the standard that the other therapies have yet to surpass. The pathologic anatomy of the goiter is determined with certainty. It carries, however, the hazard of operative accidents and complications and the general undesirability of any operation.

Students faced with the problem of choosing one from three apparently equal methods of treatment are prone to seek the solution by asking their instructor which he would choose were he to develop hyperthyroidism. With regard to the answer, it should be pointed out that not one of the three therapies is directed at the fundamental aspect of the disease. All are directed at the end organ of disease action, the thyroid gland. What is needed is a treatment directed at the stimulus that ultimately results in thyroid change. What is this stimulus?

Clinical intuition suggests that hyperthyroidism is a psychosomatic disorder — that the stimulus originates in the central nervous system. Out of the haze of clinical impressions psychiatrists are formulating a theoretical emotional pattern that under excessive strain may lead to hyperthyroidism.[124-126] Some endocrine hypersusceptibility may be basic. Evidence is overwhelming that the anterior pituitary gland is an intermediary; it is known that in conditions such as pregnancy the anterior pituitary may be unduly sensitive. Efforts to stop hyperthyroidism, however, by inhibiting the pituitary gland have been so uniformly unsuccessful that this method has had no general clinical use.[127-131] Heredity may also be a factor[132] in the hypersusceptibility.

In treating hyperthyroidism the wise clinician will take into account the possible etiology and final stimulus. He may need the help of a psychiatrist. While investigating the psychiatric and broad endocrine aspects of the disease he will maintain the patient on one of the thiouracil drugs. If a chance for readjustment of the psychologic

balance is found, the readjustment should be attempted and the drug therapy continued in the hope of obtaining a permanent remission. If no alterable social or psychiatric factor is disclosed, definitive therapy is indicated. In the patient with a life expectancy of more than twenty-five years the operative method is to be preferred.

Hyperthyroidism in Pregnancy

Pregnancy presents a special problem in the management of hyperthyroidism. Prior to 1943 miscarriage was frequent in such patients. With modern methods, survival in health of both mother and fetus should be effected. The radioactive-iodine therapy is contraindicated except in the first month or two of the pregnancy. Chapman and his co-workers[133] have shown that by the fourteenth week the thyroid gland of the human fetus absorbs the radioactive iodine. Use of radioactive iodine to reduce the size of the mother's overactive thyroid gland would also presumably sclerose and perhaps obliterate that of the fetus.

The thio- compounds have been used by some clinics as the sole therapy, with good results.[134] In the hands of others babies have been born with a goiter, in some cases large enough to obstruct the infant's airway.[135] Whether the mothers of these infants were given too much or too little of the drug is not known.[65] Until a means of avoiding this goitrogenic action in the fetus is established, it is probably wiser to use surgery as the definitive treatment for the mother's goiter and to restrict the use of the drugs to the relatively short period needed for proper preoperative preparation.

Malignant Exophthalmos

No progress has been made in our understanding of exophthalmos since the Progress Report of 1946. Progressive or malignant exophthalmos, the one fearful event of exophthalmos, continues to occur sporadically and despite all efforts. Since exophthalmos is known to be a part of Graves' disease, it is believed that a secretion of the anterior lobe of the pituitary gland is the etiologic agent.[136] There is a vast amount of experimental evidence to this effect.[137]

Exophthalmos may be progressive during the active and uncontrolled phase of Graves' disease when the metabolic rate is elevated, while the metabolic rate has been controlled at normal or when it is subnormal. The one thing that is substantial is that a subnormal metabolism is bad for exophthalmos. No matter what means is chosen to control the hypermetabolism, hypometabolism must be rigorously guarded against by administration of thyroid.

(Part II will appear in the next issue.)

References

71. Rawson, R. W., et al. Effect of iodine on thyroid gland in Graves' disease when given in conjunction with thiouracil — 2-action theory of iodine. *J. Clin. Investigation* **24**:869-877, 1945.
72. Wolff, J., and Chaikoff, I. L. Inhibitory action of excessive iodide upon synthesis of diiodotyrosine and of thyroxine in thyroid gland of normal rat. *Endocrinology* **43**:174-179, 1948.
73. Hertz, S., and Roberts, A. Application of radioactive iodine in therapy of Graves' disease. *J. Clin. Investigation* **21**:624, 1942.
74. Hamilton, J. G., and Lawrence, J. H. Recent clinical developments in therapeutic application of radio-phosphorus and radio-iodine. *J. Clin. Investigation* **21**:624, 1942.
75. Hertz, S., and Roberts, A. Radioactive iodine in study of thyroid physiology. VII. Use of radioactive iodine therapy in hyperthyroidism. *J. A. M. A.* **141**:81-86, 1946.
76. Chapman, E. M., and Evans, R. D. Treatment of hyperthyroidism with radioactive iodine. *J. A. M. A.* **131**:86-91, 1946.
77. Soley, M. H., Miller, E. R., and Foreman, N. Graves' disease: treatment with radioiodine (I^{131}). *J. Clin. Endocrinol.* **9**:29, 1949.
78. Werner, S. C., Quimby, E. H., and Schmidt, C. Clinical experience in diagnosis and treatment of thyroid disorders with radioactive iodine (8-day half-life). *Radiology* **51**:564-578, 1948.
79. Chapman, E. M., Skanse, B. N., and Evans, R. D. Treatment of hyperthyroidism with radioactive iodine. *Radiology* **51**:558-563, 1948.
80. Crile, G., Jr. *Practical Aspects of Thyroid Disease.* 355 pp. Philadelphia: W. B. Saunders Company, 1949. Pp. 106-112.
81. Soley, M. H., and Foreman, N. Radioiodine therapy in Graves' disease: review. *J. Clin. Investigation* **28**:1367-1374, 1949.
82. Crile, G., Jr. Treatment of tumors of thyroid with divided doses of radioactive iodine. *Am. J. Roentgenol.* **65**:415-419, 1951.
83. Marinelli, L. D., Trunnell, J. B., Hill, R. F., and Foote, F. W. Factors involved in experimental therapy of metastatic thyroid cancer with I^{131}; preliminary report. *Radiology* **51**:553-557, 1948.
84. Trunnell, J. B., et al. Treatment of metastatic thyroid cancer with radioactive iodine: credits and debits. *J. Clin. Endocrinol.* **9**: 1138-1152, 1949.
85. Nickson, J. J. Dosimetric and protective considerations for radioactive iodine. *J. Clin. Endocrinol.* **8**:721-731, 1948.
86. Brues, A. M. Biological hazards and toxicity of radioactive isotopes. *J. Clin. Investigation* **28**:1286-1296, 1949.
87. Robbins, L. L. Personal communication.
88. Cahan, W. G., et al. Sarcoma arising in irradiated bone: report of 11 cases. *Cancer* **1**:3-29, 1948.
89. Auerbach, O., Friedman, M., Weiss, L., and Amory, H. I. Extraskeletal osteogenic sarcoma arising in irradiated tissue. *Cancer* **4**: 1095-1106, 1951.
90. Spitz, S., and Higinbotham, N. L. Osteogenic sarcoma following prophylactic roentgen-ray therapy: report of case. *Cancer* **4**: 1107-1112, 1951.
91. Schulz, M. D., and Robbins, L. L. Dangers of irradiation of hypertrophied lymphoid tissue of the nasopharynx. *Tr. Am. Acad. Ophth.*, 1949. Pp. 243-253.
92. Evans, R. D. Quantitative aspects of radiation carcinogenesis in humans. *Unio Internat. Contra Cancrum. ACTA* **6**:1229-1237, 1950.
93. Haines, S. F., Keating, F. R., Jr., Power, M. H., Williams, M. M. D., and Kelsey, M. P. The use of radioiodine in the treatment of exophthalmic goiter. *J. Clin. Endocrinol.* **8**:815-825, 1948.
94. Henshaw, P. S., Riley, E. F., and Stapleton, G. E. Plutonium project: biologic effects of pile radiations. *Radiology* **49**:349-359, 1947.
95. Quimby, E. H., and Werner, S. C. Late radiation effects in roentgen therapy for hyperthyroidism: their possible bearing on use of radioactive iodine. *J. A. M. A.* **140**:1046, 1949.
96. Stewart, F. W. Personal communication.
97. Astwood, E. B. Treatment of hyperthyroidism with thiourea and thiouracil. *J. A. M. A.* **122**:78-81, 1943.
98. Astwood, E. B., Sullivan, J., Bissell, A., and Tyslowitz, R. Action of certain sulfonamides and of thiourea upon function of thyroid gland of rat. *Endocrinology* **32**:210-225, 1943.
99. Moore, F. D., Sweeny, D. N., Jr., Cope, O., Rawson, R. W., and Means, J. H. Use of thiouracil in preparation of patients with hyperthyroidism for thyroidectomy. *Ann. Surg.* **120**:152-169, 1944.
100. Himsworth, H. P. Thiouracil and its derivatives in routine treatment of thyrotoxicosis. *Brit. M. J.* **2**:61-64, 1948.
101. Astwood, E. B., and VanderLaan, W. P. Treatment of hyperthyroidism with propylthiouracil. *Ann. Int. Med.* **25**:813-821, 1946.
102. Bartels, E. C. Propylthiouracil: its use in preoperative treatment of severe and complicated hyperthyroidism. *Tr. Am. A. Study Goiter* 1947. Pp. 89-98.
103. Astwood, E. B. Use of antithyroid drugs in treatment of hyperthyroidism. *Tr. Am. A. Study Goiter* 1949. Pp. 210-212.
104. Himsworth, H. P., Morgans, M. E., and Trotter, W. R. Thyroidectomy and thiouracil in toxic goitre: interim comparison. *Lancet* **1**:241-243, 1947.
105. Bartels, E. C. Thiouracil and allied drugs in hyperthyroidism. *New Eng. J. Med.* **238**:6-11, 1948.
106. Morgans, M. E., and Trotter, W. R. Seasonal variations in thyrotoxicosis. *Lancet* **2**:1083, 1949.
107. McCullagh, E. P., Humphrey, D. C., McGarvey, C. J., and Sundgren, V. Results of propylthiouracil therapy for hyperthyroidism. *J. A. M. A.* **147**:106-110, 1951.
108. Iversen, K. Late results from continuous treatment of thyrotoxicosis with methylthiouracil. *J. Clin. Endocrinol.* **11**:298-311, 1951.
109. Hazard, T. P., and Eddy, R. E. Modification of sexual cycle in brook trout (*Salvelinus fontinalis*) by control of light. *Tr. Am. Fisheries Soc.* **80**:158-162, 1951.
110. Stanley, M. M., and Astwood, E. B. Determination of relative activities of antithyroid compounds in man using radioactive iodine. *Endocrinology* **41**:66-84, 1947.

111. Barrett, H. W., Goodman, I., and Dittmer, K. Synthesis of 5-halogeno-2-thiouracil and 6-methyl-5-halogeno-2-thiouracil derivatives. *J. Am. Chem. Soc.* **70**:1753-1756, 1948.

112. Williams, R. H., Towery, B. T., Rogers, W. F., Jr., Tagnon, R., and Jaffe, H. Antithyroid action of 5-iodothiouracil, 6-methyl-5-iodothiouracil, thiocytosine and (Ca) 4-n-propyl-6-oxypyrimidyl-2-mercaptoacetic acid. *J. Clin. Endocrinol.* **9**:801-817, 1949.

113. McClintock, J. C., and Lyons, J. J. A. Clinical use of iodothiouracil. New antithyroid compound. *New York State J. Med.* **51**:1633-1636, 1951.

114. Catz, B., Petit, D. W., and Starr, P. Therapeutic studies in hyperthyroidism: sodium 5-iodo-2-thiouracil. *J. Clin. Endocrinol.* **11**: 978-995, 1951.

115. Gassner, F. X., Hopwood, M. L., Herrold, E. A., and Plummer, A. J. Interpretation of goitrogenic properties of certain "antithyroid" agents. *J. Clin. Endocrinol.* **10**:1485-1498, 1950.

116. Bielschowsky, F. Tumours of thyroid produced by 2-acetyl-aminofluorene and allyl-thiourea. *Brit. J. Exper. Path.* 25:90-95, 1944.

117. Hinton, J. W., and Lord, J. W. Is surgery indicated in all cases of nodular goiter, toxic and non-toxic? *J. A. M. A.* **129**:605, 1945.

118. Payne, R. L., Crane, A. R., and Price, J. G. Thiouracil and carcinoma of thyroid. *Surgery* **22**:496-501, 1947.

119. Lahey, F. H., Bartels, E. C., Warren, S., and Meissner, W. A. Thiouracil — use in preoperative treatment of severe hyperthyroidism. *Surg., Gynec. & Obst.* **81**:425-439, 1945.

120. Curtis, G. M., and Swenson, R. E. Thiouracil and its allies in treatment of hyperthyroidism: experimental and clinical survey. *Internat. Abstr. Surg.* **86**:105-123, 1948.

121. Cattell, R. B. Surgical treatment of hyperthyroidism. *J. Clin. Endocrinol.* **9**:999-1006, 1949.

122. Cope, O., Dobyns, B. M., Hamlin, E., Jr., and Hopkirk, J. What thyroid nodules are to be feared? *J. Clin. Endocrinol.* **9**:1012-1022, 1949.

123. Beahrs, O. H., Pemberton, J. de J., and Black, B. M. Nodular goiter and malignant lesions of thyroid gland. *J. Clin. Endocrinol.* **11**:1157-1165, 1951.

124. Lidz, T., and Whitehorn, J. C. Life situations, emotions and Graves' disease. In *Life Stress and Bodily Disease*. 1135 pp. Baltimore: Williams & Wilkins Company, 1950. Pp. 445-450.

125. Ham, G. C., Alexander, F., and Carmichael, H. T. Dynamic aspects of personality features and reactions characteristic of patients with Graves' disease. In *Life Stress and Bodily Disease*. 1135 pp. Baltimore: Williams & Wilkins Company, 1950. Pp. 451-457.

126. Lidz, T., and Whitehorn, J. C. Psychiatric problems in thyroid clinic. *J. A. M. A.* **139**:698-701, 1949.

127. Means, J. H. *The Thyroid and Its Diseases*. Second edition. 571 pp. Philadelphia: J. B. Lippincott Company. Pp. 398 and 402.

128. Starr, P., and Pomerenze, H. Therapeutic studies in hyperthyroidism. *Ann. Int. Med.* **15**:226-243, 1941.

129. Foreign Letter. Paraoxypropiophenone, powerful synthetic hypophysial inhibitor. *J. A. M. A.* **145**:341, 1951.

130. Paulsen, C. A., Mortimore, G. E., and Heller, C. G. Pituitary action and estrogenic effect of parahydroxypropiophenone. *J. Clin. Endocrinol.* **11**:892-894, 1951.

131. Thompson, W. O., and Thompson, P. K. Treatment of toxic goiter by irradiation of pituitary. *J. Clin. Investigation* **23**:951, 1944.

132. Boas, N. F., and Ober, W. B. Hereditary exophthalmic goitre — report of eleven cases in one family. *J. Clin. Endocrinol.* **6**:575-588, 1946.

133. Chapman, E. M., Corner, G. W., Jr., Robinson, D., and Evans, R. D. Collection of radioactive iodine by human fetal thyroid. *J. Clin. Endocrinol.* **8**:717-720, 1948.

134. Astwood, E. B. Use of antithyroid drugs during pregnancy. *J. Clin. Endocrinol.* **11**:1045-1056, 1951.

135. Davis, L. J., and Forbes, W. Thiouracil in pregnancy: effect on foetal thyroid. *Lancet* **2**:740-742, 1945.

136. Means, J. H. Nature of Graves' disease with special reference to ophthalmic component. *Am. J. M. Sc.* **207**:1-19, 1944.

137. Dobyns, B. M. Present concepts of pathologic physiology of exophthalmos. *J. Clin. Endocrinol.* **10**:1202-1230, 1950.

MASSACHUSETTS PHYSICIANS ART ASSOCIATION

3. *Pansies*

(*Second Prize, Silver Medal, Atlantic City, 1948*)

Pencil Drawing by

J. DELLINGER BARNEY, M.D.

Formerly, Chief of Urological Service

Massachusetts General Hospital

MEDICAL INTELLIGENCE

TROPHISM VERSUS TROPISM

The following communications are published in this department rather than under Correspondence because of their peculiar etymologic significance. It is hoped that they may serve in some measure to settle the mild controversy that has refused to rage over the correct derivation and consequently the spelling of the first of the two words commonly abbreviated, after the modern alphabetical fashion into ACTH.

It is understood that the root *trophic* bears no relation to the Latin *trophaeum* (from the Greek *tropaion*), referring originally to a monument of the enemy's defeat. With or without trophies, the present decision seems to point to a victory for those who have been rallying under the trophic standard.

Tropic, on the other hand, apparently refers in any language to a turning, as of the sun in its course when it reaches those solstices designated by the crab at one extreme and the symbol for bock beer at the other.

To the Editor: There seems to be some confusion concerning whether ACTH stands for adrenocortico*tropic* hormone or adrenocortico*trophic* hormone. *The New England Journal of Medicine* accepts the latter interpretation. Such matters are eventually settled on the basis of "the usage that prevails among educated and cultured people to whom the language is vernacular" (Webster). It is therefore important that the *Journal* be set aright before its example corrupts the usage of a large number of educated and cultured physicians.

The combining form *—tropic* (Greek *tropos*, turning) has always denoted a *turning, changing* or *tending to turn or change*, especially *in a* (specified) *manner* or *in response to a* (specified) *stimulus*, as in photo*tropic*, iso*tropic* and so forth.

The stimulating effects of implants or extracts of the hypophysis on the reproductive system are due to a direct action on the testis and ovary and do not occur in the absence of these organs. The hypophysis and its extracts are therefore spoken of as exerting a gonado*tropic* action.

Hench, Kendall, Slocumb and Polley, in 1949, reported on "The effect of a hormone of the adrenal cortex . . . and of pituitary adrenocortico*tropic* hormone on rheumatoid arthritis."

The word *trophic* (Greek *trophikos*, nursing) means in English *pertaining to nutrition* and as a combining form is used in medicine in such words as hyper*trophic*, dys*trophic* and so forth. As a substitute for *-tropic*, it is an interloper.

The question is not so much one of endocrine physiology as one of etymology and orthoëpy.

ROBERT W. BUCK, M.D.

Boston, Massachusetts

To the Editor: I have investigated the question of the use of *-trophic* and *-tropic* in relation to ACTH and emerged in the same confusion with which I started. In general, most "scientific" journals, including *Endocrinology*, and most investigators have preferred the *-phic*. The American Medical Association journals and other clinical journals, including the *Journal of Clinical Endocrinology*, use *-pic*. In taking a poll of a few bibliographies on the subject, I find that *-phic* predominates somewhat but that in some journals both are used; some papers even contain both forms indiscriminately.

The reason for this confusion lies in the derivation of the two words. Trophic is from the Greek *trophikos*, which means *pertaining to nourishment* or *concerned with or regulating the nutrition* of tissues. Tropic is from the Latin *tropicus* or from the Greek *tropikos*, which means *pertaining to the turning of the sun*.

The suffix *-tropic* is from the Greek *tropos*, which means *turning* and is defined in Webster as "a combining form used to denote turning, changing or tending to turn or change in a specified manner or in response to a specific stimulus." The reason for the lack of unanimity is that ACTH, which comes from the pituitary gland, has a specific affinity for the adrenal cortex and therefore is in that sense *-tropic*. Apparently this hormone goes only to the adrenal gland. However, after reaching the gland it produces or stimulates the production of the adrenal cortical hormone or cortisone-like substance. In that sense it is *-trophic*.

From this I would say that it is entirely a matter of choice as to whether you choose one or the other and do it uniformly (perhaps it might be best to use the American Medical Association's accepted form, *-pic*) or let each author retain the form he has used in his manuscript. Perhaps someone will come out with an essay on the priority; that might settle it.

MAXWELL FINLAND, M.D.

Boston, Massachusetts

To the Editor: This is in reply to your letter of January 29 concerning the *trophic-tropic* controversy. I was glad to read the interesting letters of Dr. Buck and Dr. Finland.

My colleagues and I at the Worcester Foundation favor *trophic* in preference to *tropic*. Dr. Gregory Pincus has used *trophic* as editor of the Laurentian Hormone Conference volumes. As has been pointed out by Dr. Buck, *tropic* refers to a turning in response to a stimulus, and in biology the term *tropism* has this well understood meaning. I must, however, disagree with respect to the appropriateness of using this concept in relation to anterior-pituitary hormones. ACTH, for example, does not turn toward the adrenal cortex. It is released in the blood stream and is carried to all tissues of the body indiscriminately. When the circulation brings some of it to the adrenal cortex it acts there specifically to produce steroidogenesis and also *growth* of the gland. This enlargement of the adrenal cortex under the influence of ACTH is one of the most dramatic signs of its action.

Hypophysectomized animals, on the other hand, display adrenal atrophy, a condition that is reversible by repeated injections of ACTH. The gonadotrophins and thyrotrophic hormone also stimulate their respective target organs to growth. Since *trophic* refers to nutrition, — and growth is a consequence of enhanced nutrition, — *trophic* seems to us to be the better term, both etymologically and for reasons of common usage.

There is, it seems to me, nothing resembling tropistic action in the behavior of ACTH; it *promotes growth* of the adrenal gland, after the manner of a trophic agent. In its absence the adrenal gland displays atrophy — not atropy.

HUDSON HOAGLAND, PH.D., SC.D.
Executive Director

The Worcester Foundation for Experimental Biology
Shrewsbury, Massachusetts

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38111

PRESENTATION OF CASE

A fifty-two-year-old woman entered the hospital because of dyspnea and swelling of the legs.

One and a half years prior to admission the patient had an episode of severe substernal pain for which she was put to bed for two weeks. Following this attack she developed peripheral edema, cyanosis of the finger tips, gradually increasing dyspnea and some orthopnea. In spite of digitalis, diuretic pills, intravenous mercurial diuretics and limitation of activity, the symptoms persisted.

She stated that as a child she had always been weaker than her playmates, having been unable to keep up with their activities, and that she had had fainting spells. She further stated that she had "always had a heart murmur" and had always been somewhat short of breath; she had, however, led an active life and had gone through three pregnancies without difficulty. There was no history of rheumatic fever, scarlet fever, hypertension or any other serious illness. Except for the episode mentioned above, there had been no chest pain, fever or hemoptysis. In the year and a half prior to entry she had lost twenty-two pounds in weight.

Physical examination revealed a well developed, thin, dyspneic and orthopneic woman. There was slight clubbing and fairly marked cyanosis of the fingers. There was a marked dorsal kyphosis with anterior rotation of the left chest. The neck veins were distended. The left border of cardiac dullness was in the anterior axillary line, and there was a rumbling apical diastolic murmur with a snapping first sound. The pulmonary second sound was much louder than the aortic. There was an occasional extrasystole. A few moist rales were heard at each lung base. The liver edge was felt at the level of the iliac crest. The legs were edematous to the knees and there was thickening and pigmentation of the skin.

The temperature was 98.3°F., the pulse 80 and the respirations 20. The blood pressure was 210 systolic, 110 diastolic in both the arms and legs.

The urine, of specific gravity 1.018, gave a ++ reaction for albumin; the sediment contained a few red and white cells and an occasional granular cast. Examination of the blood showed a red-cell count of 4,400,000 and a white-cell count of 7500, with 77 per cent neutrophils. The nonprotein nitrogen was 64 mg. per 100 cc. The sedimentation rate was 2 mm. in 30 minutes and 10 mm. in 60 minutes. A blood Hinton test was negative. An electrocardiogram showed a normal rhythm at a rate of 70. The PR interval was 0.20 second and the QRS complex 0.13 second. The S waves were deep in Lead 1, the Q waves 6 mm. in Lead 3; the T waves were upright in Leads 1 and CF_4, diphasic in Lead 2 and inverted in Leads 3, CF_3 and CF_4; the ST segment was sagging in Leads 1 and 2 and depressed in Lead CF_4; the QRS complex was M-shaped in Lead CF_2. A roentgenogram of the chest showed the heart to be considerably enlarged to both sides. There was marked enlargement of the pulmonary artery and prominence of the pulmonary vascular shadow. The left auricle appeared to be enlarged. The lung fields showed no evidence of disease; there was a suggestion of a small amount of fluid in the left pleural cavity.

She was discharged after eleven days; treatment had consisted of digitalis, a low-sodium diet and Mercuhydrin. She had lost eight pounds in weight and felt much better. The nonprotein nitrogen on the day prior to discharge was 36 mg. per 100 cc.

Second admission (three years later). In the interval she did quite well on limited activity, low-salt diet, digitalis and diuretics until five months prior to admission, when she developed increased exertional dyspnea, which lasted for three to four weeks and improved spontaneously. Three weeks before admission she developed a cold with a slightly productive cough. At the same time she noted a pain in the left lateral chest wall and precordium described as "a tightness." Following this the dyspnea became more pronounced and the lips became more cyanotic. There was no ankle edema and no increase in the orthopnea. She had continued to lose weight.

On physical examination the lips and fingers were cyanotic. The neck veins were not distended at a 45° angle. The heart was unchanged from the previous admission. There were a few moist rales at the lung bases. The liver edge was just palpable on inspiration. There was no ankle edema.

The temperature was 97.5°F., the pulse 96 and the respirations 20. The blood pressure was 160 systolic, 100 diastolic.

A urine of specific gravity 1.014 gave a ++++ reaction for albumin; the sediment contained 50 red cells, 10 white cells and a rare granular and hyaline cast. Examination of the blood showed a

hemoglobin of 17.8 gm. and a white-cell count of 10,500, with 75 per cent neutrophils. A nonprotein nitrogen was 29 mg. per 100 cc. An x-ray film of the chest was unchanged from the previous admission.

The patient improved with a low-sodium diet, Mercuhydrin and digitalis and was discharged on the fifth day.

Final admission (one and a half years later — aged fifty-seven). In the interval the patient had been fairly well on limited activity and the prescribed medication; the last Mercuhydrin injection had been given one year prior to entry. She had had mild congestive failure on three occasions, each time in association with an upper-respiratory infection. The physical findings had remained unchanged. Three weeks before admission she suddenly experienced a sharp pain in the left axilla that "took her breath away." This was brief and was replaced by a constant dull gnawing ache in the same area that was unaffected by respiration or cough and was somewhat relieved by lying on the left side. There were no chills, cough, hemoptysis, perspiration, leg pain, nausea or vomiting and no change in the dyspnea or orthopnea; the cyanosis was more pronounced. She had been treated with pills and injections, including aureomycin.

Physical examination revealed a very cyanotic woman in moderate respiratory distress. The kyphosis and clubbing were as before. There was an area of dullness with crackling inspiratory rales in the left axilla. The heart was unchanged from the previous admission. There was tenderness to palpation in the right upper quadrant; the liver was not felt. There was no peripheral edema.

The temperature was 100.5°F., the pulse 100 and the respirations 40. The blood pressure was 150 systolic, 80 diastolic.

The urine had a specific gravity of 1.022 and gave a +++ reaction for albumin; the sediment contained many granular casts. Examination of the blood showed a hemoglobin of 19.3 gm. and a white-cell count of 10,900, with 87 per cent neutrophils. A chest roentgenogram showed that the heart had increased somewhat in size as compared to the previous examination, and there appeared to be some enlargement of the right interlobar artery. There was a zone of mottled density lying laterally in the left midlung, probably in the upper lobe.

The cyanosis and dyspnea increased, and the patient died quietly on the second hospital day.

Differential Diagnosis

Dr. Conger Williams*: I should like to see the x-ray films in order to see how much kyphoscoliosis there was.

Dr. James J. McCort: The first series of films were taken on the initial admission, four and a half years prior to death. The examination at that time shows a very large heart, extending to the left lateral chest wall. Both the left and right ventricles are large. The left main bronchus is elevated, and on the lower right border of the heart can be seen a double contour, which indicates enlargement of the right atrium. Therefore, the films may be said to show enlargement of the left and right ventricle and also marked enlargement of the left and right atrium (Fig. 1). Also, there is a suggestion of a small amount of fluid in the left base. Marked dilatation as well as patchy sclerosis of the pulmonary artery and its major branches is seen;

Figure 1.

the peripheral lung fields show a slight increase in vascularity. An examination of the chest made three years later shows very little change except an increase in the sclerosis of the wall of the pulmonary artery. Eighteen months later and four and a half years after the first admission the chest films show the size of the heart to have increased (Fig. 2); again there are noted marked elevation of the left main bronchus and posterior extension of a double contour on the right side, which suggest enlargement of both the left and right atria. There has also been an increase in size of the major branches of the pulmonary artery; they are one third again larger than they were eighteen months previously. The patchy sclerosis in the vessel walls is more extensive, and at this time there is a suggestion of relative avascularity of the peripheral lung fields on the right side and in the left upper lobe. In the left lower lobe there are a patch of increased density up against the lateral chest

*Associate physician, Massachusetts General Hospital.

wall and the suggestion of a small amount of fluid at the left base posteriorly.

DR. WILLIAMS: What about the degree of kyphoscoliosis? It does not look very great to me. From the protocol, I had concluded that there was a great deal of kyphoscoliosis.

DR. MCCORT: It is of a minor degree.

DR. WILLIAMS: From the protocol one would consider first a question of whether all these findings and symptoms could be attributed to the chest deformity with resultant pulmonary change. I doubted that very much after reading the protocol, and I doubt it even more after seeing these films. The patients who have pulmonocardiac failure as described by Chapman, Dill and Graybiel[1] usually have extreme kyphoscoliosis with acute angulation of the spine, which is very impressive. This patient did not have that. There are also other things in the protocol that make me doubt that kyphoscoliosis alone could account for this. One is the finding of a diastolic rumble at the apex. Even in cor pulmonale, to my knowledge, a diastolic rumble is not commonly encountered. Another point is the development of cyanosis and the gradually increasing volume of red cells, presumably in response to oxygen unsaturation, although I do not know the cause of the oxygen unsaturation. Apparently in the series of cases of kyphoscoliotic heart disease,[1] clubbing of the fingers was not present and cyanosis was not a prominent finding, so I think I am dealing with something more than scoliosis. The question is: Can this all be explained on the basis of heart disease, or must some pulmonary lesion or another complication not primarily of pulmonary origin be considered in addition to heart disease?

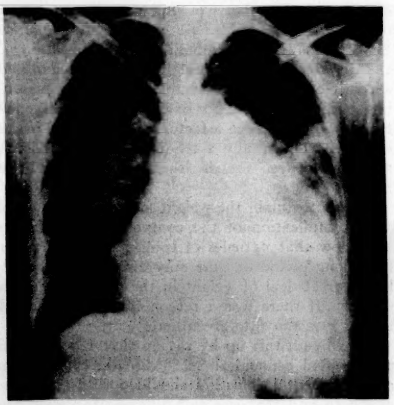

FIGURE 2.

Let me consider heart disease first. This was quite a large heart, which had increased in size steadily throughout the years of this patient's illness. The right-bundle-branch block shown in the electrocardiogram may be of some help in making the diagnosis. Although right-bundle-branch block is found in association with either mitral stenosis or cor pulmonale, it is a rather rare finding in these conditions. The electrocardiogram and the heart shadow would make me think that some element of congenital heart disease must also have been present in this patient. Of the various kinds of congenital heart disease that give cyanosis and polycythemia, tetralogy of Fallot and Eisenmenger's complex must be mentioned. There are several points against those diagnoses. One, of course, is the length of survival; an occasional patient is reported as surviving into the fifties. Moreover, I would expect, with either of these two conditions, to see early onset of cyanosis and polycythemia; here the onset of cyanosis was relatively late.

What about auricular septal defect? In the x-ray picture the diagnosis of auricular septal defect is entirely possible. There are several features that suggest it: the remarkable prominence of these hilar vessels, the prominence of the pulmonary artery and its branches, and the size of the heart in association with the finding of right-bundle-branch block in the electrocardiogram. Furthermore, auricular septal defect is compatible with long life and few symptoms until the terminal stages of the disease. It is unusual, however, to have cyanosis and polycythemia associated with that disease except under certain circumstances. With cardiac failure and an increase in right-ventricular and right-auricular pressures there may be a rare reversal of the shunt, which is normally from the left to the right auricle, so that unoxygenated blood passes from the right auricle into the systemic system through the left auricle by means of the communication. When that occurs, cyanosis may be present. This patient did go into congestive heart failure at the beginning of the illness, six years before death, and the heart failure persisted off and on.

Of course, other conditions that might produce cyanosis in the presence of an auricular septal defect should be considered. One that comes to mind is pulmonary disease itself. Did the patient have some pulmonary disease, such as pulmonary fibrosis? The many acute exacerbations of the symptoms brought on by respiratory infection make me wonder whether she actually had a widespread pulmonary fibrosis. If so, can I explain the whole picture on this basis? Did the patient have only pulmonary disease, and were the cardiac enlargement, the prominence of the pulmonary vessels and all the rest of it secondary to the pulmonary

disease, with the cyanosis and the rise in red-blood-cell count depending on arterial oxygen unsaturation? One point probably against that is the size of the branches of the pulmonary artery in the lung hilus.

One is more likely to see this in association with a septal defect. The murmur described was a mitral rumble, which is not an uncommon finding with an auricular septal defect presumably from dilatation of the right side of the heart. She did not have other auscultatory findings commonly associated with auricular septal defect, such as a loud pulmonic second sound and a diastolic blow along the left sternal border, but those are not necessarily present. Given a mitral diastolic rumble, one should think first of mitral stenosis. It was not stated whether a presystolic accentuation was present. If it were, that would make me more inclined to suspect mitral stenosis, at least as a complication here. If this were mitral stenosis alone, I would expect to find that after all these years she had developed auricular fibrillation — but of course there are exceptions to that rule.

In making a differential diagnosis between mitral stenosis and auricular septal defect, I used to be impressed by one factor: elevation of the left main bronchus in favor of mitral stenosis versus auricular septal defect. However, I found, at a clinicopathological conference[2] about a year ago, that that rule did not hold. I chose the diagnosis of mitral stenosis between the two on the basis of the elevated left main bronchus, but the patient had only an auricular septal defect. I wonder, too, whether both mitral stenosis and auricular septal defect were present in the combination called Lutembacher's syndrome. Again, I would expect to see by this time auricular fibrillation, which is a common complication. Most of the cases recently seen in this hospital in which a diagnosis of Lutembacher's syndrome was made turned out to have uncomplicated mitral stenosis or uncomplicated auricular septal defect. Mitral stenosis alone would not explain the intense cyanosis and the increasing polycythemia, which reached great heights toward the end of the illness; hence I must say that if it were present it was only a complication.

I find it difficult to fit any other congenital heart disease into this picture. I should wonder about hypertensive heart disease as a complication, and I should even wonder about the possibility of coarctation of the aorta, since the blood pressure was elevated for several years. I know nothing about the peripheral pulses in this patient; nothing in the x-ray findings permits me to make such a diagnosis. If coarctation was present, it was only a complication and would not explain this whole picture.

There are a few other conditions that ought to be considered especially as complicating factors. I was interested in the way the illness started. The patient had a bout of fever and substernal pain for which she was put to bed. She could have had coronary thrombosis obscured by the conduction defect already present in the electrocardiogram, namely, right-bundle-branch block. She could also have had pulmonary embolism. Certainly in this situation pulmonary embolism would increase the pathologic change in the lung and the tendency to cyanosis, especially if there were repeated emboli. There were two other times when she had chest pain that although not characteristic was suggestive of pleural pain. I think it is entirely possible, in spite of the absence of hemoptysis, that this patient did have repeated pulmonary emboli. One might also ask, if the hemoglobin was rising through the final illness to reach a height of 20 gm. at the end of the illness: Could she have had pulmonary thrombosis? The presence of polycythemia of that degree predisposes to thrombosis of pulmonary vessels without previous embolism. Both might exist together. She could have had embolism in the beginning of the disease with a gradual increase in cyanosis as a result of right-to-left shunt, with rising pressure in the right auricle. Poor oxygenation of pulmonary blood may have been a factor also. Increase in red-cell count and finally a tendency to thrombosis in the pulmonary vessels themselves might then result.

I cannot explain the weight loss, except as a possible complication of the congestive heart failure. We know that patients in congestive heart failure for a long period of time may lose weight, yet she lost a great deal of weight in the early part of the disease. If there was a reason for it I am unable to find it in the data given here.

I shall sum this up by saying that I believe this patient had congenital heart disease, probably an auricular septal defect. I should not be at all surprised to find that she had pulmonary emboli and even pulmonary thrombosis, and it is possible that she also had some degree of chronic pulmonary disease in the form of pulmonary fibrosis, but I would hesitate to explain this whole picture on the basis of pulmonary disease alone.

DR. ROBERT S. PALMER: How do you explain the nonprotein nitrogen? Was it just due to congestive failure?

DR. WILLIAMS: I thought the rise in nonprotein nitrogen was probably extrarenal in the first instance. I do not think I can explain all the urinary findings on the basis of polycythemia. In the tetralogy of Fallot, we sometimes see an elevated nonprotein nitrogen and albuminuria. In polycythemia the hematocrit may reach a level of 90 per cent; therefore renal filtration is interfered with and renal function may be poor to the extent of raising the nonprotein nitrogen. I wonder if the patient had a complication in the form of pyelonephritis — which might explain the hypertension also.

DR. PALMER: I shall make a diagnosis of auricular septal defect and mitral stenosis — Lutembacher's syndrome.

DR. HOWARD B. SPRAGUE: The diagnosis I had made tentatively was interauricular septal defect without mitral stenosis.

DR. PALMER: What does Dr. Sprague think a rumbling diastolic murmur at the apex means?

DR. SPRAGUE: That is very common in interauricular septal defect without mitral stenosis, as has recently been shown by Nadas[3] at the Children's Hospital and by Dr. Gordon Myers, who has looked up the cases here. It is presumably from the "Austin Flint" mechanism of a big right ventricle or from active blood flow through the septal defect.

DR. MCCORT: In support of your diagnosis of pulmonary-artery thrombosis, Dr. Williams, I would like to say that Dr. Hanelin, who has recently reviewed the cases in this hospital,[4] saw these films. He pointed out that the progressive increase in size of the pulmonary arteries with a diminished vascularity in the periphery was in keeping with a progressive thrombosis of these vessels.

CLINICAL DIAGNOSIS

Interauricular septal defect.

DR. WILLIAMS' DIAGNOSIS

Interauricular septal defect.
?Pulmonary embolism and thrombosis.

ANATOMICAL DIAGNOSES

Congenital heart disease: interauricular septal defect.
Pulmonary artery thrombosis.
Mural thrombi, right ventricle.
Enlarged right auricle.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: Just above the pulmonary valve in the main pulmonary artery was a huge thrombus, well organized, adherent to the wall and containing calcium deposits. Surrounding the well organized, apparently very old thrombus in the space between the wall of the pulmonary artery and the old thrombus was fresh thrombus. This process extended out into both branches of the pulmonary artery, so that apparently very little blood was getting into the lungs, certainly during the last admission; probably a small amount was getting in during the earliest admission. I think it is quite consistent with a duration of many years. As predicted by Dr. Williams, there was a large interauricular septal defect, which measured 4 by 3 cm. Attached to the endocardium of the right ventricle were mural thrombi, which apparently were the source of the pulmonary emboli over the years; the leg veins were normal and showed no evidence that they were at any time thrombosed. This right chamber was tremendous in size; in fact, we estimated its volume to be three times that of the left; the right ventricular wall measured 9 mm. and the left 11 mm., which is just about normal in size. The left auricle was not enlarged, but the right was voluminous. There was no disease of any valve.

The lung beyond the point of the large thrombus, or embolus with superimposed thrombus, was apparently normal. In fact, we saw very little in the smaller arteries of the lung, indicating that there probably had not been previous pulmonary hypertension associated with the auricular septal defect alone, which the patient must have had all her life. We found evidence, of course, of severe right-heart failure throughout the body. The kidney showed no change except that of congestion.

This is the third case that we have had in this hospital of the combination of auricular septal defect and major pulmonary thrombosis. Dr. Canada has gone over these cases. Have you anything to add?

DR. WILMA J. CANADA: The only thing I can add is that there are only about 5 cases in which these two conditions in combination have been reported in the literature, in spite of the fact that the number of cases of septal defect alone and pulmonary-artery thrombosis alone is high. It looks, therefore, as though their occurrence together may have been coincidental.

DR. JAMES H. CURRENS: It is of interest, Dr. Castleman, that the second patient you referred to reached the age of seventy-eight and died within the last year. He had relatively little cyanosis and no clubbing; the cyanosis was usually manifested only during cold weather. He, like this woman, manifested moderate systemic hypertension, which may have been coincidental.

DR. CASTLEMAN: Dr. Williams, do you think the thrombosis of the pulmonary artery aggravated the auricular septal defect?

DR. WILLIAMS: I should think so. Do you think it really explains the cyanosis? Do you suppose it really started by a pulmonary embolus and not a thrombus progressively increasing?

DR. CASTLEMAN: We know that with an auricular septal defect a dilatation of the pulmonary artery, often with some sclerosis, occurs, but I do not believe that the sclerosis is sufficient, — of course, you cannot be sure, — to stimulate enough of a thrombus to really build up to this. The source for embolus was found, so I think that would answer it here. That has not been true in all cases. Why there were thrombi in the right ventricle, I have no idea.

DR. WILLIAMS: Were the auricles large?

DR. CASTLEMAN: Just the right.

DR. WILLIAMS: What explained the elevation of the left main bronchus?

DR. CASTLEMAN: I wonder if the right auricle could become large enough to get over there?

DR. MCCORT: It presumably could.

DR. WILLIAMS: It occurred in the other case that I mentioned. I think it is an important point to remember.

DR. CURRENS: Dr. Nadas recently told me that about 6 per cent of patients with atrial septal defects had mitral stenosis in a sizable series of cases collected from several hospitals in Boston. If only adult cases are considered, the incidence of mitral stenosis is about 9 per cent.

REFERENCES

1. Chapman, E. M., Dill, D. B., and Graybiel, A. Decrease in functional capacity of lungs and heart resulting from deformities of chest: pulmonocardiac failure. *Medicine* **18**:167-202, 1939.
2. Case Records of the Massachusetts General Hospital (Case 36481). *New Eng. J. Med.* **243**:873-876, 1950.
3. Nadas, A. Apical diastolic murmurs in congenital heart disease. *Am. Heart J.* (in press).
4. Hanelin, J., and Eyler, W. R. Pulmonary artery thrombosis. Roentgen manifestations. *Radiology* **56**:689-702, 1951.

CASE 38112

PRESENTATION OF CASE

A seven-and-a-half-year-old girl was admitted to the hospital because of a lower-abdominal mass.

Since birth the patient had been subject to nocturnal enureses, occurring two to three times each night, and occasional enuresis during the day. Six months before admission, after having been given a laxative, she passed a stool flecked with blood. Examination at this time revealed a lower-abdominal mass, which x-ray studies showed to be indenting the bladder from above. In the interval between the discovery of the mass and admission to the hospital no further symptoms had appeared; the enuresis was unchanged.

The birth, feeding, development and past history were not remarkable; there had been no serious illnesses. The parents and two younger sisters were alive and well. The child had been born in Guatemala and lived there all her life.

Physical examination revealed a well nourished, well developed, alert, co-operative young girl in no distress. The heart and lungs were negative. Located centrally in the lower abdomen was a firm, nontender, easily palpable mass about the size of a grapefruit; its upper border was even with the umbilicus and its outline was irregular. It appeared to be somewhat fixed, but it could be palpated by ballottement on combined abdominal and rectal examination; on rectal examination the mass was palpated anteriorly. The external genitalia were normal.

The temperature was 99.8°F., the pulse 110 and the respirations 24. The blood pressure was 110 systolic, 80 diastolic.

Examination of the blood showed a hemoglobin of 14.4 gm. and a white-cell count of 6200, with 54 per cent neutrophils. The urine had a specific gravity of 1.024 and was normal. Intravenous pyelogram showed the kidneys to be normal in shape, size, position and contour; contrast substance was excreted promptly by both kidneys, and nondilated passages were seen bilaterally in normal position. A smoothly rounded mass 10 cm. in diameter extended upwards from the true pelvis anteriorly (Fig. 1). Although it could be distinguished from the bladder contour, it appeared to be closely applied

FIGURE 1. *Posterior Oblique X-Ray Film. Arrows point to calcified streaks surrounding mass.*

to its superior surface. A portion of the wall of the mass was calcified. After the bladder was emptied the mass descended further into the pelvis. A barium-enema examination showed extrinsic pressure on the rectosigmoid and on the terminal loops of ileum but no evidence of intrinsic involvement of these structures.

On the third day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. LEO B. BURGIN*: The problem here resolves itself into making a preoperative diagnosis of an abdominal mass in a seven-and-a-half-year-old female child. Since the anatomic location of the

*Associate physician to Children's Medical Service, Massachusetts General Hospital

mass influences my diagnosis greatly, I had better have a look at the x-ray films.

DR. STANLEY M. WYMAN: The examination of the chest reveals no intrinsic disease. The films selected from the examination of the colon show displacement of the sigmoid loop and of the ileum upward; however, there is no evidence of intrinsic involvement of these structures. The plain film taken before injection of contrast substance for pyelography shows an ill-defined soft-tissue fullness in the central upper pelvis overlying the sacrum. The kidneys themselves appear normal in size and shape, as nearly as one can determine. The ureters are perhaps a little wider than usual, suggesting some pressure on them. The mass is better seen after the excretion of dye, and there is seen to be a thin arcuate calcified streak in its left upper portion; this is much better seen on an oblique film taken in the right posterior oblique position. This calcified streak surrounds a fairly large portion of the mass. There is another shadow in the right anterior portion that may also be a fleck of calcification (Fig. 1).

DR. BURGIN: Can you demonstrate any pressure on the bladder?

DR. WYMAN: I think there is a little, best seen on this film from the barium-enema examination where it presses on the superior margin of the bladder and at the same time the sigmoid.

DR. BURGIN: The general good health of the patient, the normal hemoglobin, white-cell count and differential and the absence of pain and tenderness are against this being an inflammatory mass, either acute or chronic. Since the child came from Guatemala, one thinks of tropical disease — possibly an echinococcus cyst. These can exist for long periods of time without causing symptoms. The peritoneal cavity is not a common site for such a cyst, although it can occur (liver, lungs and brain are more common). There was no eosinophilia — at least none was reported in the protocol. In fact, I am not certain that hydatid disease actually occurs in Guatemala. I believe I can dismiss this possibility.

Could this have been neoplasm? The most common neoplasm in the abdomen in childhood is neuroblastoma. This tumor arises from sympathetic-nervous-system tissue in the retroperitoneal or retropleural spaces and in the adrenal glands. They are firm tumors, usually fixed and nodular. Calcification occasionally occurs. The physical and x-ray examinations suggest that this mass arose anteriorly. Since neuroblastomas are highly malignant and metastasize early and since six months had elapsed since the mass was first noted, one would expect a sicker patient, with evidence of metastases. The normal intravenous pyelogram rules out an adrenal origin for neuroblastoma, as well as the existence of the second commonest abdominal neoplasm— the embryoma of the kidney or Wilms's tumor.

I have been so impressed by the anterior position of this mass and its relation to the bladder that I have not considered too seriously the possibility of an ovarian tumor, either a simple cyst or a dermoid. The lack of sexual precocity makes a granulosa-cell tumor unlikely. Occasionally dermoids may arise from the rectovaginal septum and ride up out of the pelvis, but they usually cause more abdominal complaints — pain, rectal discomfort and so forth. The calcification noted by x-ray examination does not appear to be of the nature of bone or teeth. Tumors of the uterus in children are extremely rare and for the most part are malignant.

Mesenteric cysts, although most common in the mesentery of the small bowel, occasionally occur in the transverse mesocolon and might be felt in the midabdomen. They are generally thin-walled cysts, flabby, soft and fluctuant. Omental cysts are often difficult to distinguish from mesenteric cysts but usually lie more forward. Again, they tend to be soft, somewhat elastic and not fixed. Calcification is rarely encountered in these cysts. The location of the mass, its consistence and its intimate relation to the bladder argue against these possibilities. Although the barium-enema examination disclosed pressure on the rectosigmoid, I do not believe this was responsible for the blood-flecked stool noted in the history. The laxative could be responsible. We can be reasonably certain that there was no bleeding of any consequence subsequent to this episode, since the patient had not developed an anemia during the six months since the mass was first noted.

There is one condition that could give the picture described here — namely, a urachal cyst. As the genitourinary tract develops in the fetus, the bladder, which normally extends to the level of the umbilicus, descends along the anterior abdominal wall. The upper portion becomes elongated to form the tube-like urachus, which normally becomes obliterated; occasionally it remains patent, so that there is an escape of urine through the umbilicus. If, on the

other hand, most of the duct becomes obliterated except for a small segment, this gives rise to a cyst.

The intimate relation between the cyst and the bladder could explain the enuresis, which was both nocturnal and diurnal. Of course, enuresis is not uncommon in children who do have an abdominal mass, so this symptom may or may not be significant. We note that the mass lay between the level of the umbilicus and the superior surface of the bladder — and descended with that organ when emptied. This is just where such a cyst would be found — at the lower end of the urachus. I am a bit uneasy about the calcification. On occasion stones have been reported in such a cyst. The calcification noted may have been secondary to hemorrhage into the wall at some time. There may have been a pinpoint opening leading into the bladder at one time, and the calcification may have occurred in consequence to infection, but the history does not indicate such an episode in the past. The absence of bowel interposed between the mass and the lateral abdominal wall would be further confirmatory evidence in locating the mass in relation to the bladder. I am going to make a diagnosis of urachal cyst.

I should like to make one other comment. I think any abdominal mass in a child bears rather quick investigation. One should not spend too much time in attempting to make the diagnosis but should get the mass out.

DR. GERTRUD REYERSBACH: I think that Dr. Burgin's last remark is very pertinent. We tried to find out quickly what was the matter with this child. We were reassured when we found a normal hemoglobin and normal urine, with a history of at least seven months' illness. In making a preoperative diagnosis, we followed much the same line of reasoning as Dr. Burgin; we were surprised thereafter.

CLINICAL DIAGNOSIS

Abdominal tumor.

DR. BURGIN'S DIAGNOSIS

Urachal cyst.

ANATOMICAL DIAGNOSIS

Dermoid cyst of ovary.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: This patient was operated on by Dr. Robert R. Linton, who did not commit himself to other than abdominal tumor. The operative note seems to be very simple, almost routine, with the removal of an ovarian cyst, which proved to be a dermoid lined with skin and including hair and all the skin appendages, cholesterol crystals, sebaceous material and foci of calcification. The cyst was 10 cm. in diameter and adherent to the tube, so that it was believed not worth while to try to save either the tube or the very small part of ovarian tissue that was left. The patient has gone back to Guatemala and, I understand, is well.

A PHYSICIAN: It was not adherent to the bladder.

DR. CASTLEMAN: No.

A PHYSICIAN: May I ask the radiologist about the diagnosis of a dermoid cyst in retrospect?

DR. WYMAN: We considered the possibility of a dermoid in discussing the case at our own meeting, but I do not believe anyone thought very seriously that it was a dermoid. We did talk about urachal cyst, but I do not think we have seen calcification in the wall of a urachal cyst, as Dr. Burgin said. We thought it was a cyst that had calcification in its wall. It did not have the characteristic teeth and the characteristic radiolucency that we usually see in dermoid cysts. We could not make a definite diagnosis.

DR. CASTLEMAN: You would say the arrangement of the calcification pointed to a cystic structure of some sort.

DR. WYMAN: Yes.

The New England
Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. Richard E. Alt, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. Donald Munro, M.D.
Theodore H. Ingalls, M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR*

EDITORIAL BOARD
C. Guy Lane, M.D. Maxwell Finland, M.D.
Henry R. Viets, M.D. C. Stuart Welch, M.D.
Robert M. Green, M.D. Vernon P. Williams, M.D.
Dwight O'Hara, M.D. Benjamin Castleman, M.D.
Fletcher H. Colby, M.D. Hugh R. Leavell, M.D.
Robert L. Goodale, M.D. J. Englebert Dunphy, M.D.
Chester M. Jones, M.D. Robert W. Buck, M.D.
Harvey R. Morrison, M.D. Herrman L. Blumgart, M.D.
Deering G. Smith, M.D.†

*On leave of absence with the Armed Forces.
†Representing the New Hampshire Medical Society.

SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (medical students, $5.00 per year); Canada, $9.00 per year (Boston funds); foreign, $10.50 per year.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

MATERIAL, other than original articles, should be received not later than NOON on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

HOW FIRM THESE FOUNDATIONS?

THE past quarter of a century has been characterized by a national trend toward single-disease research and the establishment of the foundation designed to explore the problems of a specific limited field; poliomyelitis, cancer, multiple sclerosis, cardiac and mental deficiency foundations — the number could probably be expanded to at least 25, with progressive muscular dystrophy one of the newcomers. No doubt amyotrophic lateral sclerosis would be given an opportunity to show its drive appeal if it struck dread into more hearts.

Occasionally multi-million-dollar single-disease research gives rise to parodoxical situations, as, for example, when a foundation head without formal training in either clinical medicine or public health is the official spokesman to the press and to much of the country at the height of an epidemic. Recently, during the campaign of the American Heart Association, the conservative New York Times proclaimed: "King's Death Fixes Attention of World on Heart Disease." When all Britain was pondering the quasi-religious meaning of constitutional monarchy, we were told in this country that "in his death he (George VI) remains a symbol for the need for increased efforts in continuing the fight against heart disease." No doubt the already twisted significance of the King's death could have been further recast had he died during the "drive" for funds of the American Cancer Society. As recently as November, 1950, the American Research and Education Foundation for Chest Disease started a drive for $5,000,000 to find the cause and cure of the common cold (implying that the "common cold" will be found to have only *one* cause!) This was promptly followed by another proposal made at Chicago during the joint meeting of the National Safety Council and the American Academy of Pediatrics, when the establishment of a national foundation for the study and prevention of accidents was urged. The argument was advanced that such a foundation "might well result in the saving of more lives and the prevention of more disability than many of the large foundations now in existence dealing with single diseases." The contention that accidents constitute a bigger social problem than poliomyelitis, for example, is sound. More important, however, is the consideration that the most effective approach to the problem of understanding and preventing accidents has been that of scientists who do not confine their activities to "dealing with single diseases." Although some foundations have earned an enduring place in the structure of American medicine, the concept that single-disease research represents the zenith of investigational effort is profoundly shortsighted. The logical end result of this trend would be the establishment of an institute for every important unsolved problem. This would compare with the evolution of a medical specialist not only for each organ system but for each serious disease seen in private practice.

The single-disease foundation has proved effective as a money-raising device. Unfortunately, it has

occasionally proved the capacity of a tail to wag a dog. Specialization is indispensable to scientific progress. On the other hand, broadly integrated investigation and concerted application of the scientific method to whole areas of knowledge are largely responsible for the accelerated progress of medical and physical sciences since the end of the first World War. Application of this method is most dramatically embodied in the field of physics — in the success of the Manhattan Project in particular. There is an urgent need for the medical and social scientist to apply his methodology on a broad front to the pressing problems of the day. There is no reason that the investigator interested in poliomyelitis should not be interested in cancer or the common cold, or even accidents. There are many reasons that such interests should prove a stimulus to progress — a stimulus that, like the first gram of penicillin, is much more than a purchasable commodity.

CORTI AND HIS RESEARCH

From the beginning of his professional education the medical student is brought sharply into contact with the great names in anatomy. As much as the eponym is deplored by some, man is unlikely to give up his ancient habits; Scarpa's triangle, the fallopian tubes and aqueduct, Betz's cells, the fissure of Rolando and many others become familiar phrases in the dissecting room before the first term is over. Perhaps it is best for the inquiring mind not to have it otherwise. Many a lad, — and, indeed, a lassie, nowadays, — is led into the path of history via the signpost of the eponym — and who will gainsay the value of the long look back to our distinguished forebears? If such a step leads only to an awakening to the humanitarian aspects of medicine, with its old and glorious cultural past, much has been set in motion. Soon, alongside Gray, Cunningham or Piersol, come to lie modern medical dictionaries such as Blakiston's *New Gould*, Garrison and Morton's *A Medical Bibliography* and a history of medicine — Garrison's fourth edition if obtainable, or Castiglioni. The formidable blows of scientific medicine are pleasantly tempered by the softer impact of literature and history, more essential than ever in times of rapid scientific development in this atomic age.

Among the outstanding anatomists whose names are associated with a bodily structure, Alfonso Corti is one of the least known. The centennial in 1951 of the publication of Corti's description of the cochlea has led to a new evaluation of his accomplishments and the disclosure of biographical data hitherto unrecorded.[1] Son of the Marchese di Corti, whose title he inherited in later life, he was born in 1822 into a patrician family long prominent in Italian affairs. Not a few of his forebears had been physicians — one a papal physician, another a professor of medicine at Padua, Pavia and Bologna. At Pavia, where Corti studied medicine under the anatomist Panizza, he was introduced to the microscope and the new field of histology, but it was in Vienna that he finally took his degree. In Josef Hyrtl he found an ideal teacher; in the clammy gas-lit dissecting room of the Anatomical Institute he found a place to work unceasingly for more than a year. Strangely inspired, this sun-loving Italian worked without a break in the gloom and damp, receiving his degree in 1847. Appointed Hyrtl's prosector the same year, he began his study of the inner ear, using the new microtome devised by Purkinje. Revolution in Vienna caused him to carry his studies to Zurich and finally to Paris, where his mother had sought refuge. He continued his work on both the ear and the retina. The retina studies were finished first and were published in 1850. In this work he proved, using a new technic, that the cells in the retina were connected with the optic nerve.

To finish the work on the ear, Corti went to Würzburg to work under the guidance of Kölliker, foremost microscopist in Europe. Using an idea obtained from Harting of Utrecht that delicate cells should be examined suspended in fluid, Corti set to work to examine the lamina spiralis in all the mammals he could collect. Only material from man was lacking, because of the difficulty in obtaining fresh specimens. The paper was finished in Paris and sent to Kölliker for publication. Kölliker chose a journal of small circulation of which he was an editor, the *Zeitschrift für Wissenschaftliche Zoologie*, but the article was published in French, with two carefully drawn colored plates.[2] The drawings show the spiral membrane in three cross-sections

and one, in considerable detail, of the cells on its surface. Care was taken in documentation, and credit was given to Harting for his technical advice, which had been important in making Corti's study possible. A supplementary section dealt with the anatomy of the auditory nerve. It was Kölliker who, the next year, suggested the eponym *the organ of Corti*, a well-deserved tribute to his meticulous student.

One would have expected Corti, by 1851 a famous name in anatomy, to have sought a chair in a great university or at least to have continued his research. He did neither. His father having died, he and his mother left Paris and returned to the family estates. Becoming the Marchese di Corti San Stefano Belbo, he assumed his new responsibilities, married well, lived in his palace and cultivated his vineyards. His microscope forgotten and his anatomist friends neglected, Corti made only a few random observations and drawings after his epoch-making endeavor of 1851. The skyrocket, brilliant for the moment, fell to earth quickly, but the Vesalius-like drive of genius had left its mark on the world of science, so clear and distinct that all pay tribute one hundred years later to the man whose name is appropriately affixed in anatomic language.

References

1. Ullman, E. V. Life of Alfonso Corti. *Arch. Otolaryngol.* **54**:1-28, 1951.
2. Corti, A. Recherches sur l'organe de l'ouïe des mammifères. *Ztschr. f. wissensch. Zool.* **3**:109-169, 1851.

AN OLD DRUG COMES OF AGE?

In 1818 Jacob Bigelow, Rumford Professor and Lecturer on Materia Medica and Botany in Harvard University, wrote concerning *Veratrum viride:* "As a medicine or as a poisonous plant, it has been known from an early period. The aborigines of the country were fully apprized of its activity. Josselyn in his voyage to New England, which took place not long after the first settlement of the country, informs us that the young Indians had a custom of electing their chiefs by a sort of ordeal instituted with the roots of this plant, which he denominates white hellebore. A portion of this root was repeatedly given to each individual, and he whose stomach made the most vigorous resistance or soonest recovered from its effects was considered the stoutest of the party and entitled to command the rest."*

A more useful application of a "purified extract" from *Veratrum viride*, suitable for intravenous administration in acute hypertensive emergencies, is suggested in this issue. However, the use of this agent has one serious drawback. Since it is a preparation of unknown composition, its standardization depends on a biologic method. The best accuracy obtainable in such tests is of the order of ±15 per cent; frequently one must be content with ±20 per cent. Since the margin of toxicity (that is, nausea, vomiting, collapse) of purified substances from the veratrum esters is of the order of 30 to 50 per cent, it is at once apparent that the critical dosage requirements (described by Stearns and Ellis in this issue of the *Journal*) are seriously encroached on if the preparation depends for constancy of composition on biologic standardization. Since an overdosage of the drug can produce such profound and undesirable effects, it is doubtful that this agent in its present form should be used by the inexperienced.

**American Medical Botany, Being a Collection of the Native Medicinal Plants of the United States, Containing their Botanical History and Chemical Analysis, and Properties and Uses in Medicine, Diet and the Arts.* With coloured engravings. University Press, 1818.

EASTER SEAL APPEAL

The growing National Society for Crippled Children and Adults, Incorporated, with its emphasis placed particularly on the children, has announced its annual Easter Seal Appeal, which will take place this year between March 13 and April 13, ending, as usual, with Easter itself.

The Society, in preparation for its present campaign, starting today, has featured the liaison committee named by the American Medical Association to advise and counsel the Society in its program. Members of the committee include Dr. George F. Lull, secretary and manager of the American Medical Association; Dr. Edward F. McCormick, of Toledo; and Dr. Edward L. Compere, of Chicago.

. . .the man who dare stand up before the Philadelphia physicians and declare, without qualification, that "The American Medical Association is not a republican institution — it is aristocratical, both in its origin and in its continuance," *is either a bold fault-finder, or too independent for the corrupt age in which he lives.*
Boston M. & S. J., *March 17, 1852*

MASSACHUSETTS MEDICAL SOCIETY

APPLICANTS FOR FELLOWSHIP

PUBLISHED IN ACCORDANCE WITH THE PROVISIONS OF CHAPTER V, SECTION 2, OF THE BY-LAWS

BARNSTABLE

HOLLAND, CHARLES L., 475 Main Street, Falmouth.
St. Louis College of Physicians and Surgeons, 1923. Sponsor: Dr. John I. B. Vail, 155 Main Street, Hyannis.

MURAD, FRANZ RENE, Main Street, E. Brewster.
University of Vienna, 1928. Sponsor: Dr. Edward F. Briggs, Truro.

George C. Bourne, M.D., *Secretary*
67 School Street, Hyannis

BERKSHIRE

McGRATH, JOHN JOSEPH, 88 Summer Street, Adams.
University of Vermont College of Medicine, 1946.

RUBIN, IRVING, 173 First Street, Pittsfield.
Kansas City University, 1940. Sponsor: Dr. Clement F. Kernan, 184 North Street, Pittsfield.

Daniel N. Beers, M.D., *Secretary*
74 North Street, Pittsfield

BRISTOL SOUTH

DEMERS, ADELARD ALEXANDER, JR., 624 Eastern Avenue, Fall River.
Middlesex University School of Medicine, 1932. Sponsor: Dr. Francis Petrone, Fall River, 140 Winter Street.

KAUFMANN, ABRAHAM GEORGE, 58 Doris Avenue, Somerset.
Middlesex University School of Medicine, 1941. Sponsor: Dr. Samuel Manelis, 321 No. Main Street, Fall River.

MOLDIN, SIDNEY, 328 Hawthorne Street, New Bedford.
Middlesex University School of Medicine, 1944. Sponsor: Dr. Irwin Jaslow, 96 Hawthorne Street, New Bedford.

PORTNOY, NELSON L., 228 Mt. Pleasant Street, New Bedford.
Northwestern University Medical School, 1946.

RESNICK, ALBERT, 136 16th Street, Fall River.
St. Louis University School of Medicine, 1946.

James E. Fell, M.D., *Secretary*
73 Purchase Street, Fall River, Mass.

ESSEX NORTH

FREEDMAN, SANFORD TEVIA, 15 Coolidge Street, Methuen.
Tufts College Medical School, 1946.

GREENE, NICHOLAS MISPLEE, 59 Phillips Street, Andover.
Columbia College of Physicians & Surgeons, 1946.

David W. Wallwork, M.D., *Secretary*
5 Third Street, No. Andover

ESSEX SOUTH

CALL, BARBARA JOSEPHINE, 9 Oliver Street, Salem.
Tufts College Medical School, 1949.

GOWANS, JAMES DAKERS CARRIE, 10 Washington Square, Marblehead.
University of Birmingham, England, 1938. Sponsor: Dr. Charles A. Palladino, 7 Atlantic Street, Lynn.

LANDICK, ROBERT ERNEST, JR., 2 Ashton Street, Beverly.
Tufts College Medical School, 1950.

LEROYER, CHARLES PHILIP, JR., 38 Cross Street, Beverly.
Tufts College Medical School, 1942.

MacPHERSON, DONALD JUDE, 407 Lynnfield Street, Lynn.
University of Vermont College of Medicine, 1948.

Henry D. Stebbins, M.D., *Secretary*
342 Essex Street, Salem

HAMPDEN

COX, GARDNER, II, 160 Suffolk Street, Holyoke.
University of Buffalo School of Medicine, 1948.

GRUGAN, ROBERT AUSTIN, 76 Keith Street, Springfield.
Jefferson Medical College, 1946.

KRESOCK, JOSEPH WILLIAM, 113 Oakland Street, Springfield.
Temple University School of Medicine, 1945.

MONTORI, CARLO QUINTO, 18 Silver Street, Springfield.
Tufts College Medical School, 1947.

RAMAH, SIMON JOSEPH, 17 Wyman Street, Agawam.
Chicago Medical School, 1943.

WEISMAN, BERNARD, 494 East Street, Ludlow.
College of Physicians and Surgeons, Boston, 1939. Sponsor: Dr. H. Bernard Tillman, 115 State Street, Springfield.

Allen G. Rice, M.D., *Secretary*
33 School Street, Springfield

HAMPSHIRE

WIESE, FRANCES ELIZABETH PERSONS, 38 Woodbridge Terrace, So. Hadley.
Albany Medical College, 1936.

Joseph R. Hobbs, M.D., *Secretary*
Main Street, Williamsburg

MIDDLESEX EAST

BAGENSTASE, CLINTON HARRY, 424 Upham Street, Melrose.
University of Pennsylvania School of Medicine, 1940.

CARRUTHERS, RODERICK JAMES, N. E. Sanitarium and Hospital, Melrose.
College of Medical Evangelists, 1939.

DUTOIT, CHARLES HILL, 6 Perkins Road, Winchester.
Harvard Medical School, 1942.

FOLAN, DAVID WILLIAM, JR., 29 Webster Avenue, Woburn.
Tufts College Medical School, 1946.

GRADY, JOSEPH A., 291 Albion Street, Wakefield.
Georgetown University School of Medicine, 1946.

PEARSON, JOHN STROTHER, 7 Ridgefield Road, Winchester.
University of Virginia Department of Medicine, 1939.

PING, ER CHANG, 127 Hopkins Street, Reading.
Yale University School of Medicine, 1928.

William F. Hickey, Jr., M.D., *Secretary*
15 Dix Street, Winchester

MIDDLESEX NORTH

BONO, JOSEPH J., 70 Ralph Street, Lowell.
Laval University Faculty of Medicine, 1928.

COGAN, GILBERT MERRILL, 54 Pentucket Avenue, Lowell.
Tufts College Medical School, 1946.

WEINER, ROBERT SHERMAN, 62 Holyrood Avenue, Lowell.
Harvard Medical School, 1946.

Philip G. Berman, M.D., *Secretary*
174 Central Street, Lowell

MIDDLESEX SOUTH

ALMAN, RALPH WALTER, 46 Newcomb Street, Arlington.
Georgetown University School of Medicine, 1946.

BASKIES, BARNET, 380 Salem Street, Medford.
Kansas City College of Medicine & Surgery, 1938. Sponsor: Dr. J. Laurence Golden, 333 Winthrop Street, Medford.

CANDAGE, RAYMOND LESTER, 311 Salem Street, Medford.
Tufts College Medical School, 1947.

CAPRARO, SALVATORE, 261 Fellsway West, Medford.
Middlesex University School of Medicine, 1933. Sponsor: Dr. Frank Chiampa, 54 Highland Avenue, Somerville.

GODDALL, EDWIN BAKER, JR., 55 Silver Hill Road, Weston.
Harvard Medical School, 1944.

GORDON, MELVIN JACK, 459 Dudley Road, Newton Centre.
Tufts College Medical School, 1949.

GRILLONE, CAESAR P., 173 Highland Avenue, Somerville.
University of Rome Medical School, 1942. Sponsor: Dr. Ciro Giobbe, 487 Somerville Avenue, Somerville.

GURD, BARBARA CAMPBELL, 110 Holden Green, Cambridge.
Tufts College Medical School, 1947.

GUTTFELD, MARTIN, 136 Appleton Street, Cambridge.
Friedrich Wilhelms University, Breslau, 1931. Sponsor: Dr. James H. Buskirk, 330 Mt. Auburn Street, Cambridge.

KILLELEA, JOSEPH HENRY, 500 Huron Avenue, Cambridge.
Tufts College Medical School, 1944.

METCALF, JOANNA J., 4 Neal Street, Newton Lower Falls.
University of Vermont College of Medicine, 1945.
O'ROURKE, EDWARD JAMES, 253 Waverley Street, Belmont.
Harvard Medical School, 1946.
PORRECA, DANIEL ANTHONY, 232 Salem Street, Medford.
Middlesex University School of Medicine, 1939. Sponsor:
Dr. Michael C. Nash, 43 Forest Street, Medford.
RUSSO, MICHAEL DELLO, 83 Bowdoin Street, Medford.
Tufts College Medical School, 1946.
RUTENBURG, ALEXANDER MICHAEL, 21 Park Vale Avenue,
Allston.
New York University College of Medicine, 1943.
SANTELLA, JOHN JOSEPH, 61 Dalton Road, Belmont.
Middlesex University School of Medicine, 1936. Sponsor:
Dr. John F. McManus, 39 Bay State Road, Boston.
SMITH, ALECK, 30 Sunset Road, Newton.
Middlesex University School of Medicine, 1941. Sponsor:
Dr. James J. Lawlor, Otis Hospital, Cambridge.
TODD, DONALD PEARSON, 2 Broad Street, Belmont.
Harvard Medical School, 1942.
WHORISKEY, FREDERICK GILBERT, 4 Hurlbut Street, Cam-
bridge.
Tufts College Medical School, 1946.

Alexander A. Levi, M.D., *Secretary*
481 Beacon Street, Boston

MIDDLESEX WEST

AHEARN, JOHN PAUL, 14 Winthrop Street, Marlboro.
Tufts College Medical School, 1946.
HANELIN, JOSEPH, 33 Longfellow Road, Natick.
Wayne University College of Medicine, 1939.
KNOBLOCH, JOSEPH DANIEL, East Main Street, Hopkinton.
Harvard Medical School, 1943.
THAYER, THEODORE ROGERS, 97 West Central Street, Natick.
Boston University School of Medicine, 1948.

John J. Lepore, M.D., *Secretary*
96 W. Main Street, Marlboro

NORFOLK

BENARON, TULLY, 72 Rawson Road, Brookline.
University of Manitoba Faculty of Medicine, 1934.
BERENBERG, ARNOLD LESTER, 60 Gardner Road, Brookline.
Boston University School of Medicine, 1946.
BEVIVINO, BRUNO JOSEPH, 7 Fales Road, Dedham.
Kansas City College of Physicians and Surgeons, 1941.
Sponsor: Dr. Archie Abrams, 153 Dean Road, Brookline.
BLACK, THERESA ELLA, 2 Florence Street, Roslindale.
Kansas City College of Medicine, 1941. Sponsor: Dr. Wil-
liam F. Croskery, 1101 Beacon Street, Brookline.
CARTY, JOHN JOSEPH, 4 O'Leary Way, Jamaica Plain.
Tufts College Medical School, 1945.
COPEL, JOSEPH WILLIAM, 33 Naples Road, Brookline.
Tufts College Medical School, 1942.
DIETRICH, HERBERT JAMES, JR., 92 Sewall Avenue, Brookline.
Hahnemann Medical College and Hospital of Philadelphia,
1945.
DONOVAN, ALFRED MICHAEL, 61 McGreevey Way, Roxbury.
Tufts College Medical School, 1946.
EGER, WILLIAM HENRY, 97 Bloomfield Street, Dorchester.
Boston University School of Medicine, 1948.
HEIMBERG, FELIX, 81 Kingsdale Street, Dorchester.
Harvard Medical School, 1944.
HOWARD, FREDERIC MATTHEW, 681 Hammond Street, Chest-
nut Hill.
Harvard Medical School, 1940.
LOURIE, JOSEPH RICHMOND, 31 Englewood Avenue, Brookline.
Tufts College Medical School, 1940.
MAMBY, AUDLEY RICHARD, 45 Townsend Street, Roxbury.
University of Michigan Medical School, 1945.
McLAUGHLIN, JOHN CRANE, 52 Thornton Road, Brookline.
Tufts College Medical School, 1945.
MEADOWS, EDMUND CURTIS, 315 Highland Avenue, Randolph.
Harvard Medical School, 1944.
METCALFE, JAMES, 43 Wilshire Park, Needham.
Harvard Medical School, 1946.
MILLER, BENJAMIN FRANK, 217 Kent Street, Brookline.
Harvard Medical School, 1933.
MORA, RAFAEL ALBERTO, Cottage G., Payson Road, Foxboro.
Havana University School of Medicine, 1943. Sponsor:
Dr. John T. Shea, Foxboro State Hospital, Foxboro.
O'CONNOR, FRANCIS JOSEPH, 61 Thomas Street, East Ded-
ham.
Tufts College Medical School, 1951.
PENDLETON, MURRAY ETHAN, 33 Risley Road, West Newton.
Harvard Medical School, 1946.
PFEFFER, WILLIAM, JR., 356 Walnut Street, Wellesley Hills.
Harvard Medical School, 1944.
REDDEN, OLIVER BEN, 6 Mayo Avenue, Needham.
Kansas City College of Physicians and Surgeons, 1943.
Sponsor: Dr. Humphrey L. McCarthy, 479 Beacon Street,
Boston.
SALTZ, JEROME CHARLES, 294 Seaver Street, Boston.
Tufts College Medical School, 1942.
SCHAFFER, JOSEPH HOWARD, 347 St. Paul Street, Brookline.
University of Pennsylvania School of Medicine, 1946.
SCHEFF, SAUL, 163 Kent Street, Brookline.
Middlesex University School of Medicine, 1943. Sponsor:
Dr. Hyman Goldberg, 2 Pasadena Road, Dorchester.
SULLIVAN, EDMUND JOSEPH, 71 Willow Street, West Rox-
bury.
Middlesex University School of Medicine, 1941. Sponsor:
Dr. Eugene F. McDonough, 1658 Centre Street, W. Rox-
bury.
SWARTZ, JACOB, 37 Winthrop Road, Brookline.
Boston University School of Medicine, 1946.
TAYLOR, WILLIAM JOHN, Oakdale Avenue, Dedham.
Boston University School of Medicine, 1915.
THOMAS, EDWARD DONNALL, 10 Goddard Street, Sharon.
Harvard Medical School, 1946.
WOLSKY, LEONARD, 562 Centre Street, Jamaica Plain.
Harvard Medical School, 1946.

Solomon L. Skvirsky, M.D., *Secretary*
483 Beacon Street, Boston

NORFOLK SOUTH

DUBOWY, JEROME, 29 Alrick Road, Quincy.
New York University College of Medicine, 1941.
HANDY, EDWARD JOSEPH, 20 Elm Avenue, Hull.
Middlesex University School of Medicine, 1944. Sponsor:
Dr. Eugene Suzedell, 67 Coddington Street, Quincy.
PUCKO, JOSEPH JOHN, JR., 5 Old Country Way, Weymouth.
Harvard Medical School, 1945.

Ebenezer K. Jenkins, M.D., *Secretary*
Norfolk County Hospital, South Braintree

PLYMOUTH

KING, DAVID G., 49 Wellesley Road, Stoughton.
McGill University Faculty of Medicine, 1945.
INGLEE, FRANCES LANNON, 384 Market Street, Rockland.
Tufts College Medical School, 1943.
STEWART, SAMUEL KEATLY, 308 Richmond Street, Brockton.
Tufts College Medical School, 1946.
GOODWIN, CLIFTON ALLEN, 655 Washington Street, Whitman.
Middlesex University School of Medicine, 1943. Sponsor:
Dr. Andrew Mason, Newbury Street, Brockton.

Samuel Gale, M.D., *Secretary*
12 Cottage Street, Brockton

SUFFOLK

ARNOIS, DOLORES-CRYSTAL, 35 Queensbury Street, Boston.
University of California Medical School, 1946.
BROCKHURST, ROBERT JOHN, 145 Spring Street, Lexington.
Harvard Medical School, 1947.
BRODEY, WARREN MORTIMER, 39A Lee Street, Cambridge.
University of Toronto Faculty of Medicine, 1947.
CHAPLIK, ANTHONY JOHN, 65 Thomas Park, South Boston.
Tufts College Medical School, 1946.
GOADE, WILLIAM J., JR., 506 High Rock Street, Needham.
Harvard Medical School, 1944.
HORENSTEIN, SIMON, 299 Newbury Street, Boston.
University of Illinois College of Medicine, 1948.
JANCSICS, MATHEW JOSEPH, JR., 109 Quincy Avenue, E.
Braintree.
College of Physicians and Surgeons, Boston, 1944. Sponsor:
Dr. John McManus, 39 Bay State Road, Boston.
KENNEDY, BYRL JAMES, 67A Chestnut Street, Boston.
University of Minnesota Medical School, 1946.

LOWELL, ALICE, 115 Lakeview Avenue, Cambridge.
Tufts College Medical School, 1941.
MACAUSLAND, WILLIAM RUSSELL, JR., 510 E. 23rd Street, New York, New York.
Harvard Medical School, 1947.
MACK, FRANCIS LUCIAN XAVIER, 673 Union Street, Braintree.
Tufts College Medical School, 1945.
MICKLEY, JOHN HOKE, 214 Riverway Drive, Boston.
University of Maryland School of Medicine, 1932.
NARDI, GEORGE LIONEL, Massachusetts General Hospital, Boston.
University of Chicago School of Medicine, 1944.
PAPAGEORGE, WILLIAM GEORGE, 32 Bullard Street, Dorchester.
Tufts College Medical School, 1946.
TILLOTSON, FREDERICK WALTER, 323 Commonwealth Avenue, Boston.
University of Colorado School of Medicine, 1944.
WELLER, JOHN MARTIN, 55 Sherman Road, Chestnut Hill.
Harvard Medical School, 1943.
WIGGLESWORTH, WILLIAM COUNCILMAN, 20 Fernald Drive, Cambridge.
Harvard Medical School, 1944.

Charles G. Shedd, M.D., *Secretary*
1180 Beacon Street, Brookline

WORCESTER

ABBOTT, LEIGH GATES, 24 Loudon Street, Worcester.
University of Vermont College of Medicine, 1945.
APSHAGA, ALBERT ANTHONY, 13 High Street, Westboro.
Boston University School of Medicine, 1949.
ARGOFF, ARTHUR, 799 Pleasant Street, Worcester.
Laval University Faculty of Medicine, 1942.
ATWOOD, ALBERT STERLING, 1492 West Terrace Circle, Teaneck, New Jersey.
Yale University School of Medicine, 1945.
BIANCHI, JOHN LAWRENCE, 4 Norman Avenue, Worcester.
Tufts College Medical School, 1950.
BUTLER, CARROL FRANCIS, 81 Kenwood Avenue, Worcester.
Georgetown University School of Medicine, 1944.
ELLIS, RICHARD GEORGE, 295 Maple Avenue, Shrewsbury.
Hahnemann Medical College, 1945.
FOLEY, JOHN JOSEPH BREEN, 35 Beaver Street, Worcester.
Tufts College Medical School, 1950.
GARDNER, PAUL JOSEPH, 23 Varnum Street, Worcester.
Boston University School of Medicine, 1947.
HAMMOND, ROBERT LEE, 88 Morningside Road, Worcester.
Long Island College of Medicine, 1946.
SILKMAN, ROBERT JOSEPH, 70 Grandview Avenue, Worcester.
Tufts College Medical School, 1946.
SPEAR, IVAN MACDONALD
McGill University Faculty of Medicine, 1945.
TRACY, THOMAS HENRY, 2 Oak Street, Worcester.
Tufts College Medical School, 1950.
SCHUR, WALTER ROBERT, Charlton Street, Oxford.
Middlesex University School of Medicine, 1940. Sponsor: Dr. Adolph Meltzer, 44 Cedar Street, Worcester.
SCHUH, MARIE MUELLER, Belmont Hospital, Worcester.
College of Physicians and Surgeons, Boston, 1947. Sponsor: Dr. Arthur Ward, 7 Bellevue Avenue, Worcester.

Edward Budnitz, M.D., *Secretary*
57 Cedar Street, Worcester

WORCESTER NORTH

BABINEAU, ROBERT ALBERT, 192 Pearl Street, Fitchburg.
Boston University School of Medicine, 1946.
JACQUES, RAYMOND BECHARD, 193 Water Street, Fitchburg.
Laval University School of Medicine, 1944.
LEHNDORFF, PETER GEORGE, 56 Prospect Street, Fitchburg.
University of Vienna School of Medicine, 1937. Sponsor: Dr. H. J. Sparling, 46 Merriam Parkway, Fitchburg.
SCHAFFNER, GILBERT FRANK, Gardner State Hospital, E. Gardner.
Middlesex University School of Medicine, 1941. Sponsor: Dr. W. P. Cordes, Gardner State Hospital, E. Gardner.

Seymour I. Nathanson, M.D., *Secretary*
882 Main Street, Fitchburg

CORRESPONDENCE

ENDOTRACHEAL INTUBATION

To the Editor: I have read with interest the carefully prepared article by Dr. Benjamin Etsten and Dr. Donald Mahler on "Subglottic Membrane, a Complication of Endotracheal Intubation" that appeared in the *Journal* for December 20, 1951.

Their general conclusions seem to me to be sound. This article raises, however, several questions that were not discussed but could with advantage be brought out for discussion, since endotracheal intubation is so widely used, and rightly so.

It is my belief that many anesthetists use endotracheal tubes that are needlessly large, — too large, — in diameter. Size 29F or 32F is large enough for nearly all normal adults. We have shown that these comparatively small tubes allow normal gas exchange; both arterial oxygen and arterial carbon-dioxide tensions are maintained at normal levels when these tubes are used (*Anesthesiology* **11**:730, 1950). These tubes lie free in the airway without pressure on the trachea, except for their weight. When positive pressure in the airway is essential, as in open thoracic surgery, the necessary airtight airway can be obtained with a well fitting face mask.

The current general lack of interest in tube size is perhaps reflected in the omission of any mention of the size of the tubes used in the article of Etsten and Mahler, although much other detail is provided.

Certainly inflatable cuffs on endotracheal tubes have some uses. Either they or pharyngeal packs (it has not yet been definitely shown which is better) are important during esophageal surgery. When the esophagus is tented up by the surgeon, the positive pressure in the airway is then thrown into the esophagus and, toward the end of the procedure, onto the new suture line. This should be avoided. Furthermore, when purulent or irritating material in the pharynx must be kept out of the lungs, as during the incision of a pharyngeal abscess, inflatable cuffs are useful. They are not, however, generally essential, even in thoracic surgery, — other than that mentioned, — and are certainly not needed in abdominal surgery.

Remarkably enough, a tube is now on the market that is designed to be wedged in the airway so that an airtight fit is established. In the cases referred to by Drs. Etsten and Mahler the comment was made that the system was "airtight" even without the inflation of the cuff. Surely any large tube or cuff, let alone one with an airtight junction, is bound to produce trauma of the delicate lining of the airway, with every breath the patient draws. Since a cuff is rarely necessary, — and then only for very short periods, — it would seem to be inviting trouble to use tightly fitting tubes or cuffs as a general practice when there is no specific need of them.

Damage of the type described here is not limited to the subglottic region. Dr. Cameron Haight of the University of Michigan has told me that some years ago he bronchoscoped a six-year-old girl after the use of an inflatable cuff on an endotracheal tube. He found a cast of the trachea at the junction of the middle and lower thirds of the trachea. In another case he found on bronchoscopy a cast of the trachea in the middle portion after the insertion of an endotracheal tube into a trachea narrowed by pressure from a substernal thyroid gland.

Damage of this kind is potentially fatal. Except for careful, watchful handling, as in the three cases described by Drs. Etsten and Mahler, death might have ensued. Finally, it is impossible to know how often or for how long damage occurs to a ring of cilia around the trachea when inflatable cuffs or tight endotracheal tubes are employed. The cilia are known to be very sensitive to trauma; they are also known to be important in clearing the airway of extraneous material. The assumption appears justified that such damage is common and important and needless in most cases. In conclusion, endotracheal tubes are a very important adjunct in anesthesia. On infrequent occasions inflatable cuffs attached to them are important. The use of cuffs or needlessly large tubes augments the hazard described by Drs. Etsten and Mahler.

HENRY K. BEECHER, M.D.
Boston, Massachusetts

BOOK RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

IATA Bulletin: Official record of the proceedings of the International Air Transport Association. (No. 13, June 1951.) Montreal, International Air Transport Association, 1951. $2.00 a copy, or $3.75 per year (United States), or the equivalent in other currencies.

This bulletin, published occasionally, contains material of medical interest on sanitary regulations and the medical committee of the organization.

NOTICES

SOUTH END MEDICAL CLUB

The next luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, March 18, at noon.

The speaker will be Dr. J. G. Kuhns, chief of the Orthopedic Staff at Robert Breck Brigham Hospital and visiting orthopedic surgeon at the Boston Children's Hospital. His subject will be "The Treatment of Arthritis in the Aged." All physicians are invited to attend.

POSTGRADUATE COURSE IN OBSTETRICS AND PEDIATRICS

As previously announced, the Postgraduate Course in Obstetrics and Pediatrics conducted by the Boston Lying-in Hospital and the Children's Hospital, with the co-operation of the Massachusetts Department of Public Health, will be held April 17-19.

There will be no registration fees. Interested physicians may communicate with Dr. Crawford H. Hinman, 221 Longwood Avenue, Boston 15.

PROGRAM

Thursday, April 17 (Boston Lying-in Hospital)
9:00 a.m. Registration (Lecture Hall)
9:30 a.m. Dr. A. T. Hertig. Implantation, Placentation and Abortion
10:00 a.m. Dr. W. L. Caton, Jr. Clinical Aspects of Placental Physiology
10:30 a.m. Dr. R. H. Barker. Clinical and X-Ray Evaluation of the Obstetrical Pelvis
11:00 a.m. Dr. C. A. Smith. Influence of Nutrition on Pregnancy and the Newborn
11:30 a.m. Dr. A. G. Gauld. Controversial Aspects of the Conduct of Labor
12:00 m. Dr. A. T. Hertig and Dr. D. G. McKay. Clinical Pathological Conference
1:00 p.m. Luncheon Discussion (Cafeteria). Drs. Reid, Janeway, Brugler and Rice and Mr. R. D. Mills
2:00 p.m. Dr. H. B. Nelson and Dr. P. White. Pregnancy Complicated by Diabetes
2:30 p.m. Dr. S. L. Romney. The Status of the Search for Specific Treatment of Toxemia
3:00 p.m. Dr. M. F. Eades. Delivery of the Potentially Infected Patient
3:30 p.m. Dr. D. E. Reid. Last-Trimester Bleeding
4:30 p.m. Dr. L. K. Diamond. Advances in Isosensitization

Friday, April 18 (Boston Lying-in Hospital)
8:00 a.m. Dr. D. E. Reid and Dr. T. R. Goethals. (1) Ward Rounds — 4th floor; Visiting Obstetrician. (2) Cesarean Section — 4th floor. Dr. S. H. Clifford and Dr. C. A. Smith. (3) Rounds — Premature Nursery
9:30 a.m. Dr. G. P. Sturgis. Clinic on Medical Problems in Obstetrics (Lecture Hall)
10:30 a.m. Dr. C. A. Smith. Practical Aspects of the Care of the Premature and Newborn
11:00 a.m. Dr. S. H. Clifford. The Management of Medical and Surgical Problems of the Premature and Newborn
11:45 a.m. Question-and-Answer Period
12:00 m. Dr. A. T. Hertig. Clinical Pathological Conference
1:00 p.m. Lunch (Cafeteria)

Friday, April 18 (Main Amphitheatre, Children's Hospital)
Discussions relating to the first six months of life
2:00 p.m. Dr. S. Dooley. Nutrition Requirements and Infant Feeding
2:30 p.m. Dr. P. Patterson. Failure in Normal Growth and Development
3:00 p.m. Dr. H. Shwachman. Treatment of Acute Bacterial Infections
3:30 p.m. Dr. A. Nadas. Congenital Heart Disease
4:00 p.m. Dr. L. Longino. Urgent and Elective Operative Procedure
4:30 p.m. Dr. R. Smith. Anesthesia, Office and Operating Room
5:00 p.m. Dr. D. Grice. Orthopedic Problems

Saturday, April 19 (Jimmy Fund Building, Binney Street)
9:00 a.m. Dr. R. C. Eley. Immunization Procedures
9:30 a.m. Dr. L. K. Diamond. Anemia
10:00 a.m. Dr. D. Matson. Neurosurgical Disturbances
10:45 a.m. Recess Period
11:00 a.m. Question-and-Answer Period

BOSTON DISPENSARY PROCTOLOGIC SESSION

An all-day scientific session, with round-table luncheon discussion and evening banquet, sponsored by the Proctologic Group of the Boston Dispensary, will be held at the Hotel Kenmore, Boston, May 10. The meeting is open to both specialists and general practitioners. Further information may be obtained from Dr. John F. Keane, 122 Commonwealth Avenue, Boston (Telephone KE 6-6872).

THE SPRINGFIELD HOSPITAL

The educational program of the Springfield Hospital for the month of April is as follows:

Wednesday, April 2
11 a.m.–12 m. Psychosomatic Medicine — Group Therapy. Drs. Calvert Stein and J. Graham Bruce. Staff Room.

Saturday, April 5
10–11 a.m. Surgical Grand Rounds.
11 a.m.–12 m. Combined Medical-Surgical Grand Rounds with Panel Discussion on "The Management of Degenerative Diseases of the Spinal Cord," with Dr. Allen S. Johnson as Moderator. Discussers: Drs. Joseph Hahn and William Corwin. Staff Conference Room.

Wednesday, April 9
11 a.m.–12 m. Psychosomatic Medicine — Group Therapy. Drs. Calvert Stein and J. Graham Bruce. Staff Room.

Thursday, April 10
12:15 p.m. Staff Meeting. Staff Room.

Saturday, April 12
10–11 a.m. Surgical Grand Rounds.
11 a.m.–12 m. Clinicopathological Conference. Staff Conference Room.

Tuesday, April 15
8:30 p.m. Guest-Speaker Conference, in the Staff Conference Room, on "Endometriosis." Dr. Joe V. Meigs, chief gynecological surgeon, Vincent Memorial Hospital, and clinical professor of gynecology, Harvard Medical School.

Wednesday, April 16
11 a.m.–12 m. Psychosomatic Medicine — Group Therapy. Drs. Calvert Stein and J. Graham Bruce. Staff Room.

Saturday, April 19. Holiday.

Wednesday, April 23
11 a.m.–12 m. Psychosomatic Medicine — Group Therapy. Drs. Calvert Stein and J. Graham Bruce. Staff Room.

Saturday, April 26

10–11 a.m. Surgical Grand Rounds.

11 a.m.–12 m. Combined Medical and Surgical Death Reviews. Staff Conference Room.

Wednesday, April 30

11 a.m.–12 m. Psychosomatic Medicine — Group Therapy. Drs. Calvert Stein and J. Graham Bruce. Staff Room.

LONG ISLAND COLLEGE OF MEDICINE

The annual Alumni Day of the Long Island College of Medicine and the State University of New York at New York City College of Medicine will take place on April 26. A scientific session at Polhemus Clinical Hall will be followed by the annual business meeting. There will be interfraternity activity in the afternoon. The seventy-second annual dinner will be held at the Columbus Club, 1 Prospect Park West, Brooklyn, at 7:00 p.m.

POSITIONS IN NEW YORK STATE

The New York State Education Department has two openings in Albany at a starting salary of $6449 for doctors with experience as school physicians and knowledge of school health-service programs.

The positions, those of senior supervisors of school medical service (general), pay salaries up to $7804 after five years of service.

The State Civil Service Department is now accepting applications from any qualified citizen of the United States. Applicants must have or be eligible for a New York State license to practice medicine and must also have had two years of experience in the practice of medicine, including service as a school physician.

The positions, which require considerable traveling, involve putting into action various rules and regulations in the field of school health service. The duties include visiting local schools and aiding them in their school health programs.

No written or oral examinations will be given. Candidates will be rated on their education and professional experience.

Further information may be secured from the State Department of Civil Service, State Office Building, Albany. Applications will be accepted for an indefinite period.

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS

The sixty-third annual meeting of the American Association of Genito-Urinary Surgeons will be held at the Seaview Country Club, Absecon, New Jersey, June 19-21.

FRANK E. BUNTS EDUCATIONAL INSTITUTE

On April 3, 4 and 5, 1952, the Frank E. Bunts Institute and the Cleveland Clinic Foundation will present a continuation course for physicians on "The Diagnosis and Treatment of Malignant Disease." Dr. Freddy Homburger, research professor of medicine at Tufts College Medical School, will give the evening lecture on April 4. The other guest speakers will be Dr. Allan C. Barnes, professor of obstetrics and gynecology at Ohio State University College of Medicine; Dr. Brown M. Dobyns, associate professor of surgery at Western Reserve University School of Medicine; and Dr. Thomas D. Kinney, director of laboratories at Cleveland City Hospital and professor of pathology at Western Reserve University School of Medicine. Inquiries may be addressed to the Frank E. Bunts Educational Institute, 2020 East 93rd Street, Cleveland 6, Ohio.

PAN-AMERICAN CONVENTION OF GASTROENTEROLOGY

The third Pan-American Convention of Gastroenterology will be held in Mexico City from May 11 to May 17.

Further information may be obtained from the Secretary General, Dr. Ramón Flores López, Oficina de Enseñanza e Ivestigación Científica del Hospital General, Mexico 9, D. F.

INTERNATIONAL CONGRESS OF DIETETICS

The First International Congress of Dietetics will be held July 7 to 11 in the Royal Tropical Institute, Amsterdam, Netherlands. Interested persons may apply for further details to Miss Diane J. Ten Haaf, General Secretary, Executive Committee, 13 Pomonaplein, The Hague, Netherlands.

SOCIETY MEETINGS AND CONFERENCES

March 3–April 30. Seventh Postgraduate Lecture Course. Page 274, issue of February 14.

March 13 and 14. International College of Surgeons. Page 354, issue of February 28.

March 13 and 27. Alcoholism Staff Conference. Quincy City Hospital. 1:30–3:00 p.m.

March 18. South End Medical Club. Page 433.

March 18–29. Springfield Hospital. Page 316, issue of February 21.

March 19–26. Lahey Clinic Fellowship Teaching Program. Page 160, issue of January 24.

March 23, 28, and 29. Massachusetts Association of Medical Technologists, Inc. Page 354, issue of February 28.

March 24. Annual Lecture of Sigma (Temple) Chapter of Phi Delta Epsilon Fraternity. Page 316, issue of February 21.

March 24–27. American Academy of General Practice. Page 354, issue of February 28.

March 24–28. American College of Chest Physicians. Page 160, issue of January 24.

March 25 and April 24. Norfolk District Medical Society. Page 710, issue of November 1.

March 26. Boston Gastroenterological Society. Page 354, issue of February 28.

March 29 and 30. American Psychosomatic Society. Page 390, issue of March 6.

March 31–April 4. Fifth American Congress on Obstetrics and Gynecology. Page 832, issue of November 22.

April 2. Tufts Medical Alumni Association. Page 354, issue of February 28.

April 2–30. Springfield Hospital. Page 433.

April 3–5. Frank E. Bunts Educational Institute. Notice above.

April 5 and May 3. New England Society of Anesthesiologists Postgraduate Education Course. Page 996, issue of December 20.

April 7–9. American College of Allergists. Page 390, issue of March 6.

April 10. Mistakes in Diagnosis of Angina Pectoris and Coronary Occlusion. Dr. Howard B. Sprague. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

April 14–25. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

April 15. Massachusetts Society for Research in Psychiatry. Page 792, issue of November 15.

April 17–19. Boston Lying-in Hospital and Children's Hospital. Postgraduate Course in Obstetrics and Pediatrics. Page 433.

April 21–25. Cancer Seminar. Page 114, issue of January 17.

April 23. Massachusetts Academy of General Practice. Springfield.

April 23. New England Obstetrical and Gynecological Society (Spring Meeting). Hartford, Connecticut.

April 25 and 26. Texas Medical Center. Page 354, issue of February 28.

April 26. Alumni Association of the Long Island College of Medicine. Notice above.

May 3. Annual meeting. Massachusetts Association of Medical Technologists, Inc. Page 433.

May 10. Boston Dispensary Proctologic Session. Page 433.

May 10 and 11. American Electroencephalographic Society. Page 390, issue of March 6.

May 11–17. Pan-American Convention of Gastroenterology. Notice above.

May 19–23. Courses in Laboratory Diagnosis of Tuberculosis. Page 354, issue of February 28.

May 20–22. Massachusetts Medical Society. Hotel Statler, Boston.

May 26–28. Minnesota State Medical Association. Annual Meeting. Page 316, issue of February 21.

May 26–29. National Tuberculosis Association. Copley Plaza and Statler hotels, Boston.

June 5–8. American College of Chest Physicians. Page 280, issue of February 14.

June 18–20. Massachusetts Public Health Conference. Amherst.

June 19–21. American Association of Genito-Urinary Surgeons. Notice above.

July. Commonwealth and Empire Health and Tuberculosis Conference. Page 792, issue of November 15.

July 7–11. International Congress of Dietetics. Notice above.

July 7–12. International Diabetes Federation. Page 316, issue of February 21.

July 8–11. Thirteenth British Congress of Obstetrics and Gynaecology. Page 916, issue of December 6.

(*Notices concluded on page xix*)